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PRELIMINARY ENVIRONMENTAL HAZARD ASSESSMENT OF CHLORINATED NAPHTHALENES, SILICONES, FLUOROCARBONS, BENZENEPOLYCARBOXYLATES, AND CHLOROPHENOLS

Syracuse University Research Corporation

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A review of five classes of chemical compounds covering production, environmental exposure, environmental effects, health effects, and toxicology. The classes covered are benzenepolycarboxylates (including phthalates), chlorinated naphthalenes, chlorophenols, silicones (siloxanes), and fluorocarbons (including chlorofluorocarbons). The report contains extensive references.

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See attached sheet

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Chlorine aliphatic compounds
Chlorine aromatic compounds

Fluorine organic compounds
Fluorine aliphatic compounds
Dichlorodifluoromethane
Fluoroalkanes
Fluorohydrocarbons

Naphthalene compounds

Phenols

Siloxanes
Silicon organic compounds
Silicones

Production capacity
Marketing
Utilization
Toxicity
Chemical properties
Toxicology
Occupational diseases
Pollution

This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

ABSTRACT

A literature search of pertinent information and data on chlorinated naphthalenes, silicones, fluorocarbons, benzenepolycarboxylates, and chlorophenols was conducted to determine any hazard to man or the environment from commercial use of these chemicals. Information was gathered on physical and chemical properties, production and usage, environmental contamination, monitoring and analysis, environment transport and fate, environmental effects, and toxicity.

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TABLE OF CONTENTS

Page

ABSTRACT i

CHLORINATED NAPHTHALENES

- I. Physical Properties 1
- II. Production 3
- III. Uses 3
- IV. Current Practice 5
- V. Environmental Contamination 6
- VI. Monitoring and Analysis 7
- VII. Chemical Reactivity 10
- VIII. Biology 11
  - A. Absorption 11
  - B. Excretion 11
  - C. Transport 11
  - D. Distribution 12
  - E. Metabolic Effects 12
  - F. Metabolism 12
- IX. Environmental Transport and Fate 13
  - A. Persistence and/or Degradation 13
  - B. Environmental Transport 16
  - C. Bioaccumulation 16
- X. Toxicity 17
  - A. Human Toxicity 17
  - B. Toxicity to Birds and Non-Human Mammals 20
    - 1. Acute and Subacute Toxicity 21
    - 2. Chronic Toxicity: Rats and Rabbits 25
      - a. Mono- and Mono/Di- Combinations 25
      - b. Dichloronaphthalene 26
      - c. Tri- and Tri/Tetra- Combinations 26
      - d. Tetra/Penta- Combinations 27
      - e. Penta and Penta/Hexa- Combinations 27
      - f. Hexachloronaphthalene 29
      - g. Heptachloronaphthalene 29
      - h. Octachloronaphthalene 29
    - 3. Sensitization 29
    - 4. Teratogenicity 30
    - 5. Carcinogenicity 30
    - 6. Mutagenicity 30
    - 7. Behavior Effects 30
  - C. Toxicity to Lower Animals 30
  - D. Toxicity to Plants 30
  - E. Toxicity to Microorganisms 30
- XI. Summary and Conclusions 32
- Literature Cited 35

Table of Contents (continued)

Page

SILICONES (SILOXANES)

- I. Physical Properties 39
  - A. Silicone Fluids 40
  - B. Silicone Rubbers 43
  - C. Silicone Resins 43
- II. Production 45
- III. Uses 49
  - A. Silicone Fluids 49
    - 1. Waxes and Polishes 49
    - 2. Cosmetics 50
    - 3. Urethane Foams 50
    - 4. Silicone Greases 50
    - 5. Silicone Emulsions 50
    - 6. Other 51
    - 7. New Applications 52
  - B. Silicone Rubbers (Elastomers) 52
  - C. Silicone Resins 54
- IV. Current Practice 56
- V. Environmental Contamination 57
- VI. Monitoring and Analysis 58
- VII. Chemical Reactivity 60
- VIII. Biology 62
  - A. Absorption 62
  - B. Excretion 62
  - C. Transport and Distribution 63
- IX. Environmental Transport and Fate 66
  - A. Persistence and/or Degradation 66
  - B. Environmental Transport 67
  - C. Bioaccumulation 68
- X. Silicone Toxicity 69
  - A. Human Toxicity 69
    - 1. Occupational Exposure 69
    - 2. Liquid Injection of Silicones 69
    - 3. Toleration by the Human Eye 70
    - 4. Degeneration of Silicone Heart Valves 70
    - 5. Adverse Responses to Other Medical Silicones 71
    - 6. Human Ingestion 72
  - B. Toxicity to Birds and Non-Human Mammals 72
    - 1. Acute and Subacute Toxicity 72
    - 2. Chronic Toxicity 77
    - 3. Sensitization 78
    - 4. Teratogenicity 78
    - 5. Carcinogenicity 79
    - 6. Mutagenicity 79
    - 7. Behavior Effects-Reproductive Activity 80

Table of Contents (continued)

Page

C. Toxicity to Lower Animals 82
D. Plant Toxicity 84
E. Microorganism Toxicity 84
XI. Silicones: Summary and Conclusions 85
Literature Cited 90

FLUOROCARBONS

I. Physical Properties 95
II. Production 98
III. Uses 101
IV. Current Practices 104
V. Environmental Contamination 104
VI. Monitoring and Analysis 105
VII. Chemical Reactivity 108
VIII. Biology 111
A. Absorption 111
B. Excretion/Elimination 113
C. Transport 115
D. Distribution 116
E. Metabolism 116
F. Metabolic Effects 118
IX. Environmental Transport and Fate 121
A. Persistence and/or Degradation 121
B. Environmental Transport 122
C. Bioaccumulation 122
X. Toxicity 123
A. Human Toxicity 123
1. Acute Inhalation 123
2. Chronic Inhalation 126
3. Ingestion 127
4. Polymer-Fume Fever 127
B. Toxicity to Non-Human Mammals 128
1. Acute and Subacute Toxicity 128
2. Chronic Toxicity 137
3. Sensitization 139
4. Teratogenicity 139
5. Carcinogenicity 140
6. Mutagenicity 140
7. Behavioral Effects 140
C. Toxicity to Lower Animals 142
D. Toxicity to Plants 142
E. Toxicity to Microorganisms 142
XI. Fluorocarbons: Summary and Conclusions 144
Literature Cited 147

Table of Contents (continued)

Page

BENZENEPOLYCARBOXYLATES 153

- I. Physical Properties 155
- II. Production 157
- III. Uses 160
  - A. Phthalic Acid (PA) and Phthalic Anhydride (PAN) 160
  - B. Isophthalic Acid 164
  - C. Terephthalic Acid (TA) and Dimethyl Terephthalate (DMT) 165
  - D. Trimetllitic Acid (TMA) and Trimellitic Anhydride (TMAN) 166
  - E. Trimesic Acid (TMSA) 166
  - F. Pyrometllitic Acid (PMA) and Pyromellitic Dianhydride (PMDA) 166
- IV. Current Practice 167
  - A. Phthalic Anhydride 167
  - B. Isophthalic Acid 167
  - C. Terephthalic Acid and Dimethyl Terephthalate 167
  - D. Trimellitic Anhydride 168
  - E. Pyromellitic Dianhydride 168
- V. Environmental Contamination 169
- VI. Monitoring and Analysis 171
- VII. Chemical Reactivity 173
- VIII. Biology 176
  - A. Absorption 176
  - B. Excretion 176
  - C. Transport 177
  - D. Distribution 177
  - E. Metabolism 178
  - F. Metabolic Effects 179
- IX. Environmental Transport and Fate 180
  - A. Persistence and/or Degradation 180
  - B. Environmental Transport 182
  - C. Bioaccumulation 182
- X. Toxicity 183
  - A. Human Toxicity 183
  - B. Toxicity to Birds and Non-Human Mammals 185
    - 1. Acute and Subacute Toxicity 185
      - a. Phthalic Anhydride 185
      - b. Phthalic, Isophthalic, and Terephthalic Acids 186
      - c. Trimellitic Acid and Anhydride 190
    - 2. Chronic Toxicity 191
    - 3. Sensitization 192
    - 4. Teratogenicity 192
    - 5. Carcinogenicity 192
    - 6. Mutagenicity 193
    - 7. Behavioral Effects 193

Table of Contents (continued)

Page

C. Toxicity to Lower Animals 193
D. Toxicity to Plants 193
E. Toxicity to Microorganisms 193
XI. Benzenepolycarboxylates: Summary and Conclusions 194
Literature Cited 198

CHLOROPHENOLS

I. Physical Properties 204
II. Production 206
III. Uses 210
  A. *o*-Chlorophenol 210
  B. *p*-Chlorophenol 210
  C. 2,4-Dichlorophenol 212
  D. 2,6-Dichlorophenol 212
  E. 2,4,6-Trichlorophenol 213
  F. 2,4,5-Trichlorophenol 213
  G. 2,3,4,6-Tetrachlorophenol 214
  H. Pentachlorophenol 214
  I. 4-Chloro-*o*-cresol 215
  J. Others 215
IV. Current Practice 216
V. Environmental Contamination 217
VI. Monitoring and Analysis 220
VII. Chemical Reactivity 222
VIII. Biology 223
  A. Absorption 223
  B. Excretion 224
  C. Transport 224
  D. Distribution 225
  E. Metabolism 226
  F. Metabolic Effects 227
IX. Environmental Transport and Fate 230
  A. Persistence and/or Degradation 230
  B. Environmental Transport 235
  C. Bioaccumulation 236
X. Toxicity 237
  A. Human Toxicity 237
  B. Toxicity to Birds and Non-Human Mammals 240
    1. Acute Toxicity 240
    2. Chronic Toxicity 244
    3. Sensitization 245
    4. Teratogenicity 245
    5. Carcinogenicity 245
    6. Mutagenicity 245
    7. Behavioral Effects 245

Table of Contents (continued)

Page

C. Toxicity to Lower Animals 245
D. Toxicity to Plants 247
E. Toxicity to Microorganisms 249
XI. Chlorophenols: Summary and Conclusions 253
Literature Cited 256

LIST OF FIGURES

Figure Page

I. Chlorinated Naphthalenes

1 Vapor Pressure of Chlorinated Naphthalene 1
2 Metabolism of Chlorinated Naphthalene and Benzene 14
3 Proposed Mechanisms for Naphthalene Dihydrodiol Formation in Mammalian and Microbial Systems 15

II. Silicones

1 Viscosity-Temperature Curves for Various Silicones 41

III. Fluorocarbons

1 Concentration of Some Halogenated Hydrocarbons in Alveolar Air After Various Times of Breath Holding 111
2 Possible Metabolic Pathways of Halothane 117
3 Effect of Halothane on Bioluminescence of P. phosphoreum 143

IV. Benzenepolycarboxylates

1 Equilibrium Between Benzenecarboxylic Acids and Anhydrides 174
2 Equilibrium Between Benzenecarboxylic Acid and Its Anion Conjugate 175
3 Metabolism of Phthalic Acid 180

V. Chlorophenols

1 Synthetic Routes to Chlorophenols and Chlorophenol By-Products 211
2 Pentachlorophenol Transport in the Mouse 224
3 Suggested Metabolic Fate of PCP in Rats 226
4 Oxidation of Hydroxy- and Chlorophenols 232
5 Relationship Between the Logarithm of the Solubility of Chlorophenols and the LD_{50} in Lemna minor 248
6 Relationship Between the Logarithm of the IC_{50} and the Solubilities of Some Chlorophenols 250

Table of Contents (continued)

LIST OF TABLES

Table Page

I. Chlorinated Naphthalenes

I. Comparative Properties of Halowax Chloronaphthalenes 2
II. Uses of Chlorinated Naphthalenes 4

II. Silicones

I. Physical Properties of Some Technical Methylsilicone and Methylphenylsilicone Oils 40
II. Vapor Pressure of Silicone Fluids 42
III. Production of Silicone Resins and Elastomers 46
IV. Estimated Silicone Usage in U.S. Market - 1973 48
V. Silicone Rubber Usage by Market: 1964 54
VI. Consumption of Silicone Resins (1962) 55
VII. Distribution of ^{14}C-Labeled Silicone in Rat Tissues 25 Days after Intraperitoneal Injection of 15 μCi per Rat 64
VIII. Distribution of ^{14}C-Labeled Silicone in Rat Tissues 45 Days after Intracisternal Injection of 6 μCi per Rat 64
IX. Mortality and Response Resulting from the Administration of Silicone Fluids in Single Oral Dose -- Guinea Pigs 73
X. Comparative Relative Activities of 32 Organosiloxane Compounds Based on Effects on the Ovariectomized Immature Female Rat Uterus 81
XI. Daphnia Mortality (%) in SAG 10 and SAG 530 Solutions 83

III. Fluorocarbons

I. Physical Properties of Commercially Important Fluorocarbons 96
II. Typical Physical Properties of Polytetrafluoroethylene 97
III. Fluorocarbon Producers and Capacities 99
IV. Production and Capacities of Fluorocarbons 100
V. Uses of Fluorocarbons 102
VI. Electron-Capture Detector Response to Various Fluorinated Compounds 109
VII. Elimination of Fluorocarbons in Dogs' Breath 114
VIII. Inhalation Toxicity of Fluoromethanes 129
IX. Dose/Effect Relationship for CCl_2F_2 and CCl_3F 130
X. Cardiac Sensitization to Epinephrine 130
XI. Acute Inhalation Toxicity of Several Fluoroethanes 133
XII. Comparison of Bromine and Chlorine in the Acute Inhalation Toxicity of Fluoroethanes 134

Table of Contents (continued) (Tables)

III. Fluorocarbons (cont.)

Table — Page

XIII. Inhalation Toxicity of Several Fluoroalkenes 135
XIV. Inhalation Toxicity of Several Halogenated Alkenes 135
XV. LC_{50} for DCHFB
XVI. Delayed Death after DCHFB Administration to Rabbits 137
XVII. Chronic Exposure to Some Fluorocarbons Showing no Pathology 138
XVIII. Tumors Induced in Swiss Mice by Injection of "Freons" and Piperonyl Butoxide Shortly After Birth 141

IV. Benzenepolycarboxylates

I. Physical Properties of Commercially Important Benzenepolycarboxylates 156
II. Production of Benzenepolycarboxylates 158
III. Capacities for Production of Benzenepolycarboxylates 159
IV. Phthalic Anhydride Consumption - 1968 160
V. Intermediates and Dyes Produced from Phthalic Anhydride 162-3
VI. Consumption of Isophthalic Acid 164
VII. Contaminants in Phthalic Anhydride Process Off-Gas 169
VIII. Excretion of Terephthalic Acid after the Oral Administration of a Single Dose of 85 mg/kg to Rats 177
IX. Distribution of Terephthalic Acid after a Single Oral Dose of 85 mg/kg 178
X. Inhibition of cis-Aconitase by Various Benzenepolycarboxylic Acids at 10 mM 179
XI. Biodegradibility of Several Phthalates and Other Organic Compounds Using a River Die-Away Test 181
XII. Toxicity of Benzenedicarboxylic Acids to Mice 24 Hours after Intraperitoneal Injection 186
XIII. Lethal Doses for Terephthalic Acid by Intraperitoneal Injection of Mice 187
XIV. Acute Toxicity of Terephthalic Compounds in Mice and other Mammals 189
XV. Acute Oral Toxicity (LD_{50}) of TMA and TMAN to Mice and Rats 190

V. Chlorophenols

I. Physical Properties of Commercially Important Chlorophenols 205
II. Chlorophenol Producers and Their Plant Locations and Capacities 207
III. Production of Chlorophenols and Related Products 208

Table of Contents (continued) (Tables)

V. Chlorophenols (cont.)

Table		Page
IV.	Analytical Techniques Used for the Determination of Chlorophenols in Trace Amounts	221
V.	Distribution of Pentachlorophenol in Three Cases of Fatal Intoxication	225
VI.	Metabolic Effects of Pentachlorophenol and Their Possible Physiological Significance	228
VII.	Inhibition of Oxidative Phosphorylation by Various Chlorophenols	228
VIII.	50% Inhibition of Catalase Activity by Various Chlorophenols	229
IX.	Microbial Decomposition of Chlorophenols in Soil Suspensions	231
X.	Decomposition of Phenol and Chlorophenol by a Soil Microflora	233
XI.	Maximum Degradation Obtained for Each Compound at 100 mg/liter	233
XII.	LC_{50}'s of Various Chlorophenols and Sodium Chlorophenates after a Single Oral Administration	241
XIII.	Acute LD_{50}'s of Chlorophenols Determined by Intraperitoneal Injection to Male Albino Rats	242
XIV.	Comparison of LD_{50}'s for Intraperitoneal Injection in Rats to 24 Hour TLm of Fishes	246
XV.	Median Tolerance Limits of Some Fresh Water Fishes to Sodium Pentachlorophenate	247
XVI.	LD_{50}'s of Various Chlorophenols on *Lemna minor*	248
XVII.	Concentrations of Various Chlorophenols Required for 50% Inhibition of Radial Growth (IC_{50}) for *T. viride*	250
XVIII.	Antimicrobial Efficiencies of Pentachlorophenol (Dowicide EC-7)	251

CHLORINATED NAPHTHALENES
(HALOWAXES)

I. Physical Properties

In general, the physical properties of the Halowaxes are dependent upon the degree of chlorination. The mono- and dichloronaphthalenes are liquids at room temperature whereas the higher chlorinated compositions are solids. As the chlorine content increases the specific gravity, boiling point, melting point, fire and flash point all increase while the vapor pressure and water solubility decrease. The following table provides a comparison of the properties of Halowaxes. The vapor pressures of the various isomers are shown in Figure 1.

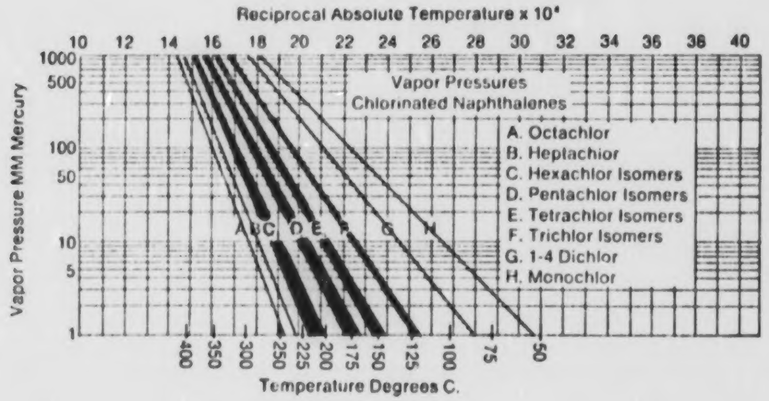


Figure 1. Vapor Pressure of Chlorinated Naphthalene (Koppers, a); reprinted by permission.

Table I. Comparative Properties of Halowax Chloronaphthalenes (Koppers, a); reprinted by permission

PRODUCT NUMBER		1031	1000	1001	1099	1099B	1013	1014	1051	2141	2148
1 Composition		Mono-Chlor	Mono- + Di-Chlor	Tri- + Tetra-Chlor	Tri- + Tetra-Chlor	Tri- + Tetra-Chlor	Tetra- + Penta-Chlor	Penta- + Hexa-Chlor	Octa-Chlor	Blend	Blend
2 Physical Form		Liquid	Liquid	Flakes	Flakes	Flakes	Flakes	Flakes	Powder	Cakes	Flakes
3 Chlorine Content, % (Approximate)		22	26	50	52	52	56	62	70	54	61
4 Specific Gravity	@ 25°C	1.20	1.22	1.58	1.59	1.65	1.67	1.78	2.00	1.62	1.76
	@ 60°C	—	—	—	—	—	—	—	—	—	—
5 Initial Boiling Points	@ 30 MM	144°C	144°C	200°C	205°C	212°C	222°C	242°C	310°C	—	—
	@ 100 MM	180°C	180°C	234°C	241°C	248°C	258°C	278°C	—	—	—
	@ 760 MM	250°C	250°C	308°C	315°C	322°C	329°C	344°C	—	—	—
6 Distillation Range		5% Max. 255°C	—	—	—	—	—	—	—	—	—
		95% Min. 265°C	80% Min. 282°C	—	—	—	—	—	—	—	—
		98% Min. 275°C	90% Min. 300°C	—	—	—	—	—	—	—	—
7 Softening Point (Melting Point), °C (Approx.)		—25	—33	93	102	115	120	137	185	135	103
8 Flash Point, °C, C.O.C.		135	130	200	210	210	230	250	None to 430	—	250
9 Fire Point, °C, C.O.C.		165	170	None to Boiling	None to Boiling	None to Boiling	None to Boiling	None to Boiling	None to Boiling	—	None to Boiling
10 Specific Heat, Gm. Cal./Gm./°C		— —	0.40 @ 50° 0.42 @ 100°	0.22 @ 15° 0.65 @ 100°	— —	— —	— —	0.19 @ 15° 0.48 @ 100°	— —	— —	— —
11 Latent Heat of Vaporization, Cal./Gm.		—	100.4 @ 250°C	—	—	—	—	—	—	—	—
12 Color		White to Pale Straw	White to Pale Straw	White to Pale Yellow	White to Pale Yellow	Light Yellow	Light Yellow	Light Yellow	Light Yellow	Gray White	Light Yellow
13 Acidity, Maximum (Mg. of KOH/Gm.)		0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.1	0.05	0.1
14 Viscosity, Saybolt Univ. Sec. (Approx.)		35 @ 25°C	34 @ 25°C	30 @ 130°C	31 @ 130°C	31 @ 130°C	33 @ 130°C	35 @ 150°C	—	183 @ 190°C	—
15 Volatility	200 Gms. with Surface 9.5 Sq. in. for 10 Days @ Room Temp.	1.0%	1.5%	—	—	—	—	—	—	—	—
	Gms./Sq. in./Hr. @ 105°C	—	—	0.010	—	—	0.005	0.001	—	0.06 @ 140°C	0.001
16 Penetration, 200 Gm., 5 Secs. @ 25°C (Approx.)		—	—	—	—	—	—	—	—	24	11
17 Dielectric Constant		—	—	25°C 100°C	25°C 100°C	25°C 115°C	25°C 130°C	25°C 150°C	—	25°C	—
	@ 60 Cycles/Sec.	—	—	— 4.1	— 4.1	— 4.0	4.8 3.8	4.4 3.7	—	3.8	—
	@ 1000 Cycles/Sec.	—	—	5.3 4.1	5.3 4.1	5.3 4.0	4.8 3.8	4.4 3.7	—	3.8	—
18 Power Factor	@ 60 Cycles/Sec.	—	—	— 0.37	— 0.37	— —	0.002 0.45	0.0008 0.99	—	0.0006	—
	@ 1000 Cycles/Sec.	—	—	0.002 0.005	0.002 0.005	0.002 .01	0.0003 0.04	0.0002 0.44	—	0.0002	—
19 Resistivity, Megohm Centimeters		—	—	Over 1×10^9 1×10^6	Over 1×10^9 1×10^6	Over 1×10^9 1×10^9	Over 1×10^9 1×10^6	Over 1×10^9 1×10^6	—	Over 1×10^9	—

II. Production

In the United States the sole producer of chlorinated naphthalenes is the Koppers Company, Inc. The chemicals are sold under the trade name of Halowaxes. Other international manufacturers of chlorinated naphthalenes are Bayer in Germany (Nibren waxes) and the Imperial Chemical Industries Ltd. in the United Kingdom (Seekay waxes); Crow (1970) has stated that presently in the United Kingdom only small firms produce the chemicals and only chlorinated naphthalenes with four chlorines or less.

Koppers produces their Halowaxes at a plant in Bridgeville, Pennsylvania, a few miles outside of Pittsburgh. In 1972 the market for chlorinated naphthalenes was less than 2.27×10^8g (5 million lbs.) (Koppers, c). This is down from the 1956 total output of about 3.24×10^8g (7 million lbs.) (Hardie, 1964). Hardie (1964) has suggested that this decline in use is due to their serious disadvantages such as their toxic nature in handling.

III. Uses

Table II lists the various Halowax compositions, number of chlorines, percentage of the market and principal commercial use. The tri- and tetrachloronaphthalenes (Halowax 1001 & 1099) make up more than half of the United States market. They are used as an impregnate in automobile capacitors. Automobile capacitors are often changed during car engine tune ups. The second largest part of the market is the mono- and dichloronaphthalenes (Halowax 1000 & 1031) which are mostly used as an oil additive to clean sludge and petroleum deposits in engines, although

Table II. Uses of Chlorinated Naphthalenes (Koppers, c)

Halowax	% of Chlorinated Isomers	% Market* (1972)	Uses
1000 1031	60% 1 Cl, 40% 2Cl 95% 1 Cl, 5% 2Cl	15-18%	Engine oil additive to dissolve sludge and deposits
1000 1031	60% 1 Cl, 40% 2 Cl 95% 1 Cl, 5% 2 Cl	~10%	Used in fabric dyeing industry.
1001} 1099}	{10% 2 Cl, 40% 3 Cl {40% 4 Cl, 10% 5 Cl	65-66%	Impregnate for automobile capacitors.
1013 1014	10% 3 Cl, 50% 4 Cl, 40% 5 Cl 20% 4 Cl, 40% 5 Cl, 40% 6 Cl	~8%	Mostly for electroplating stopoff compounds, also impregnate for carbon electrodes used for chlorine production.
1051	10% 7 Cl, 90% 8 Cl	.5%	Unknown

---

*Based on a market of less than 2.27×10^8g (5 million lbs.)

they find some use in the fabrics dyeing industry. The highly chlorinated naphthalenes are used mostly as electroplating stopoff compounds, but only in relatively small quantities.

A comparison of the market volume and types of use of chlorinated naphthalenes to that of PCB's provides some insight into the relative hazard of chlorinated naphthalenes due to release into the environment. In 1970, the largest sales year, 73 million lbs. of PCB's were sold; in contrast the chlorinated naphthalene market was less than 5 million lbs. in 1972. Nisbet and Sarofim (1972) have reviewed the various uses of PCB's to determine estimates of the quantities discharged into the environment. Use of PCB's in capacitors (mostly for fluorescent lights) amounted to 26 million lbs. as compared to less than 3.25 million lbs. for chlorinated naphthalenes capacitor use. The cited authors estimated that a large proportion of the PCB's capacitors ultimately were deposited in a dump or landfill. PCB's annual use for hydraulic fluids and lubricants amounts to approximately 7 million lbs. and was suggested as a major source of water contamination. Chlorinated naphthalene use as an oil additive amounts to less than 0.8 million lbs. Other uses of PCB's such as plasticizers and heat exchangers, which have been cited as major sources of air and water contamination, are not uses of chlorinated naphthalenes.

IV. Current Practice

The high thermal stability and resistance to chemical attack of chlorinated naphthalenes reduces any instability problems which might otherwise be encountered during packing and transport. The liquid chlorinated naphthalenes (Halowax 1031 & 1000) are usually shipped and stored in 55 gallon steel drums and occasionally they are transported in tank cars. The higher chlorinated solids are usually shipped in small quantities (<50 lbs.) in fiber pack containers.

The manufacturer recommends that equipment using the Halowaxes be enclosed and fumes and vapors be exhausted; individuals having a history of skin disease, liver disorders, or alcoholism should not be employed; work clothing should be completely supplied including close-weave coveralls, socks, caps, underwear, gloves, and aprons and the clothing should be changed twice a week; and face and hands should be washed before eating and a shower taken upon quitting work (Koppers, b).

V. Environmental Contamination

Although a number of researchers have recognized the similarity between the physical and chemical properties and uses of PCB's and chlorinated naphthalenes (Armour and Burke, 1971; Goerlitz and Law, 1972) and have developed analytical procedures for low-level detection in the environment (see section on Monitoring & Analysis), no report of chlorinated naphthalene contamination of the environment has been cited. In most cases the analytical procedures were developed to assure that chlorinated naphthalenes were not interfering with analysis for PCB's or organochlorine pesticides such as DDT. Some of the analytical techniques developed, especially gas chromatographic-mass spectrometry, would allow for the detection and quantification of chlorinated naphthalenes in environmental samples. However, no study specifically directed at detection of chlorinated naphthalenes in the environment has been reported, although the development of the analytical techniques suggests that some researchers may have attempted such analysis.

In the early 1950's chlorinated naphthalenes were found as a contaminant in pelletized feed and they were the principal cause of a man-made disease called bovine hyperkeratosis (Olson, 1969). This contamination was due to the use of a lubricant containing chlorinated naphthalenes in machines for pelletizing feed. The contamination and disease is rarely encountered today.

Chlorinated naphthalenes have also been detected as a contaminant in foreign commercial PCB formulations (Phenochlor and Clophen), although they were not detected in domestic formulations (Aroclor) (Vos et al., 1970).

VI. Monitoring and Analysis

Bovine hyperkatosis resulting from contamination of commercial protein concentrates led to the development of monitoring techniques for chlorinated naphthalenes. Reber et al. (1956) extracted the protein concentrate with methanol and fractionated the ether-soluble fraction on an alumina column. Quantification was obtained by a combination of colorimetric, ultraviolet absorption, and infrared absorption procedures. However, the sensitivity of this method would not be sufficient for trace analysis of environmental samples as is shown by the fact that the authors worked with a sample that contained 150 mg of chlorinated naphthalene, a huge amount compared to the ng and μg quantities usually obtained from environmental samples.

Vos *et al*. (1970) have reported the use of gas chromatographic-mass spectrometric and microcoulometric analysis for detection of impurities in commercial samples of PCB's. Hexa- and heptachloronaphthalenes were detected in some of the commercial products in the ppm range using that method.

Armour and Burke (1971) first recognized that chlorinated naphthalenes may interfere with the gas chromatographic determination of several organochlorine pesticides. They had previously developed a method for separating PCB's from pesticides (Armour and Burke, 1970) and, thus, were interested in determining the behavior of chlorinated naphthalenes in the FDA multipesticide residue methods (Food & Drug Administration, 1969).and the silicic acid column chromatography method developed for PCB's (Burke and Armour, 1970). Results showed that chlorinated naphthalenes would interfere using the FDA cleanup (Florisil column chromatograph) whereas the silicic acid·cleanup method would completely separate the chlorinated naphthalenes from the organochlorine pesticides. With the silicic acid column the chlorinated naphthalenes would be recovered in the same eluant as PCB's. Holmes and Wallen (1972) found similar results with a column of silica gel eluted with hexane. They were able to remove the possible interference of chlorinated naphthalenes from PCB's by the selective oxidation of the chlorinated naphthalenes with chromic acid.

Goerlitz and Law (1972) studied which chlorinated naphthalene isomers might possibly interfere with gas chromatographic analysis of pesticides (assuming no column chromatographic cleanup). They pointed out that the electron capture chromatographic pattern of compounds and isomers for commercial Halowax preparations is not as distinct as for PCB's, thus making it much more difficult to recognize interferences. Their results show that insecticides lindane, heptachlor, aldrin, p,p'-DDE, p,p'-DDD and p,p'-DDT elute closely to major Cl_3, Cl_4, Cl_5, and Cl_6 chlorinated naphthalenes. The authors suggest three methods of assuring that chlorinated naphthalenes do not interfere with the pesticide analysis: (1) processing every sample through a scheme such as described by Armour and Burke (1971); (2) compare the response of a component on electron capture and microcoulometric or conductivity detectors; and (3) use gas chromatographic-mass spectrometry. Rote and Morris (1973) have discussed how PCB's, chlorinated naphthalenes, and polychlorinated terphenyls can be distinguished with GC-MS.

Stalling and Huckins (1973) have used reverse phase thin layer chromatograph (RPTLC) with components of Aroclors, Halowaxes, and several chlorinated pesticides. The spots were recovered and characterized by gas chromatography or gas chromatographic-mass spectrometry. The spot patterns of individual Aroclors and Halowaxes were reproducible and characteristic but, in the case of Halowaxes, the spots were not completely resolved into individual components as determined by gas chromatography. The method appears to be quite useful when the contaminant is an individual commercial formula and GC-MS is not available. With mixtures of commercial products or mixtures of Aroclors and Halowaxes, its utility would be somewhat reduced.

VII. Chemical Reactivity

Chlorinated naphthalenes, like PCB's, exhibit a high degree of chemical and thermal stability indicated by their resistance to most acids and alkalies and resistance to dehydrochlorination (Koppers, a). For example, 1-chloronaphthalene, at moderate temperatures, is unaffected by water and alkali and only decomposes to 1-naphthol after prolonged heating with caustic soda at temperatures above 300°C (Hardie, 1964). The higher chlorinated naphthalenes are stable to most oxidizing agents and at 120-125°C in a dry atmosphere are unaffected by copper or mild steel. In the presence of moisture at 120-125°C, they tarnish copper, due to the liberation of small amounts of hydrogen chloride (Hardie, 1964).

Chlorinated naphthalenes are not as stable as PCB's to oxidation by chromic acid. Holmes and Wallen (1972) have used this difference in resistance to oxidation to eliminate chlorinated naphthalenes from interfering with gas chromatographic detection of PCB's. The product from chromic acid oxidation is a chlorine substituted phthalic acid (Hardie, 1964). This does not necessarily mean that chlorinated naphthalenes would be oxidized in the environment, since well-known persistent environmental pollutants, such as p,p'-DDE, are oxidized with chromic acid treatment (Holmes and Wallen, 1972).

VIII. Biology

The biology of toxic compounds are usually discussed in terms of their toxic behavior. Consequently, the following topics have received only cursory attention in the literature.

A. Absorption

Three natural routes are available for the intake of chlorinated naphthalenes: ingestion, inhalation, and cutaneous absorption. Of these, inhalation seems to be a primary route in occupational exposure with fumes sublimating and reaching relatively high concentrations at temperatures far below that of boiling (Crow, 1970). While cutaneous absorption is common, it usually results in far less severe pathological effects (Bennet, 1938). Collins (1943) noted no indications of such entry in the handling of cold chloronaphthalene solids. In domestic animals, ingestion is by far the most common route and results in the most severe pathology (Olson, 1969; Huber and Link, 1962).

B. Excretion

In the surveyed literature, male rats were the only subjects used to study the excretion of chlorinated naphthalenes (Cornish and Block, 1958). The lower chloronaphthalenes do not appear to be excreted unchanged. About 20% of hepta- and penta-chloronaphthalens were found to be excreted in the urine and feces.

C. Transport

No studies focusing on chloronaphthalene transport were encountered. It seems reasonable to assume from the abundant toxicological data and metabolic study (Cornish and Block, 1958) that, regardless of the route of entry, an appreciable amount of chlorinated naphthalenes are transported to the liver where they are metabolized, excreted and/or stored. Orally, chlorinated naphthalenes may be transported unaltered along the digestive tract and be excreted in the feces (Cornish and Block, 1958).

D. Distribution

Again, clinical or experimental data are not available. The liver is a probable site of chlorinated naphthalene accumulation.

E. Metabolic Effects

The primary metabolic effect of the chlorinated naphthalenes is to interfere with the metabolism of carotene and its transformation to Vitamin A as reflected in decreased plasma Vitamin A (Olson, 1969). Also, 1,4-dichloronaphthalene has been found to increase the activity of O-demethylase in the liver of rats (Wagstaff, 1971). The Vitamin A effect is highly variable. Goats, sheep, swine, mice, chickens and rats are much less susceptible than cattle (Olson, 1969). The species specific variations in the carotene-Vitamin A metabolism necessitates caution in interpreting these findings (Hansel and McEntee, 1955).

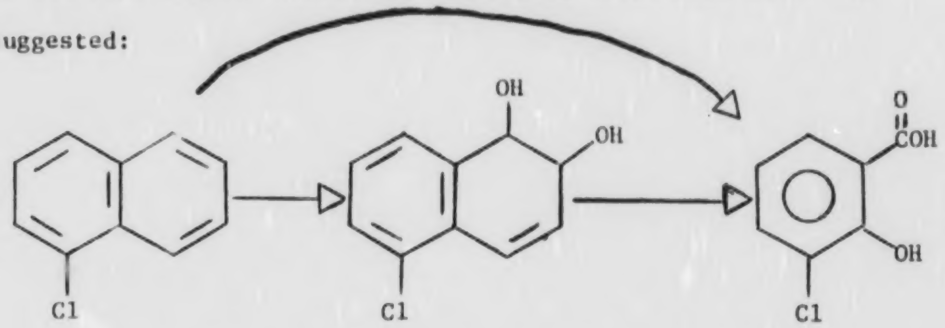
F. Metabolism

Only one study has been encountered that attempts to describe the metabolism of various chlorinated naphthalenes. Testing for the presumed metabolites in rat urine, Cornish and Block (1958) concluded that the mono- to tetra- were able to be metabolized to some extent. The more highly chlorinated naphthalenes, however, were not so metabolized. The possibility of alternative pathways and tissue accumulation was proposed but not investigated.

IX. Environmental Transport and Fate

A. Persistence and/or Degradation

Environmental decomposition of chlorinated naphthalenes has received little study. Only the monochlorinated naphthalenes have been studied under biological conditions similar to those found in the environment. Walker and Wittshire (1955) have examined the decomposition of both 1-chloro- and 1-bromonaphthalene by soil bacteria. They found that five strains of bacteria, obtained from soil, would grow in a mineral salts medium with 1-chloronaphthalene as the sole carbon source. The following metabolism route was suggested:



Similar results were found for the 2-chloronaphthalene by Canonica and coworkers (1957).

Okey and Bogan (1965) examined the rate of metabolism of 1-chloro and 2-chloronaphthalene by bacteria that were first grown on unsubstituted naphthalene (see Figure 2). The initial concentration of chlorinated substrates was 1 mg/ℓ and the substrate was the only source of carbon.

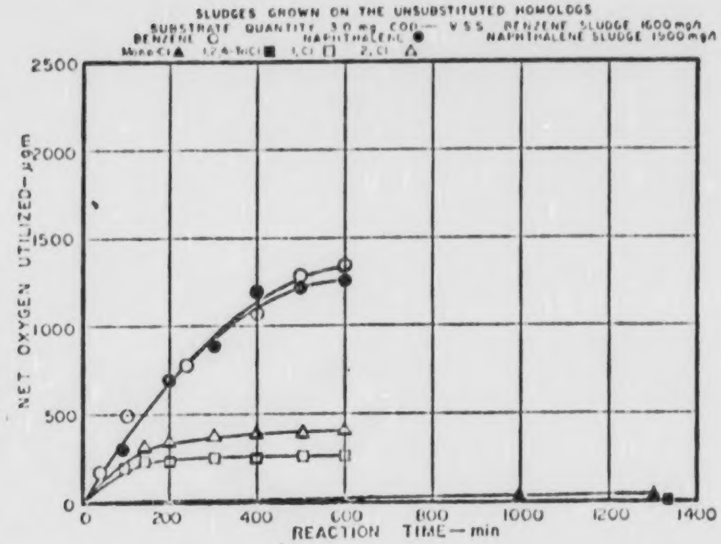


Figure 2. Metabolism of chlorinated naphthalene and benzene [Okey and Bogan, 1965]; reprinted by permission of publishers of Journal Water Pollution Control Federation.

The following relative rates of metabolism were observed: naphthalene>>>2-chloronaphthalene>1-chloronaphthalene.

The microbial degradation of the highly chlorinated naphthalenes has not been studied. However, their metabolism in mammalian systems (rabbit) has been examined by Cornish and Block (1958). They administered 1 gm quantities of naphthalene and chlorinated naphthalenes (1-chloro, di-, tetra-, penta-, hepta-, and octachloronaphthalenes) to male albino rabbits and collected 24-hour urine samples daily for a 4-day period. Each urine sample was analyzed for creatinine, glucosiduronic acids, phenolic compounds, sulfur partitions, and mercapturic acid and in the case of penta- and heptachloronaphthalenes for the unchanged parent molecule. These researchers concluded that

1-chloro and dichloronaphthalene are readily metabolized by the rabbit; tetrachloronaphthalene is metabolized somewhat slower; and penta-, hepta-, and octachloronaphthalene do not undergo the usual metabolic reactions to the measured end products. For penta- and heptachloronaphthalenes only 20% of the 1 gm dose was excreted in an unchanged form during the 4-day period. Correlation of these *in vivo* results to environmental microbial metabolism is questionable. Gibson (1972) has suggested that the initial reactions in these two systems (mammalian and microbial) are quite different as is depicted in the following figure.

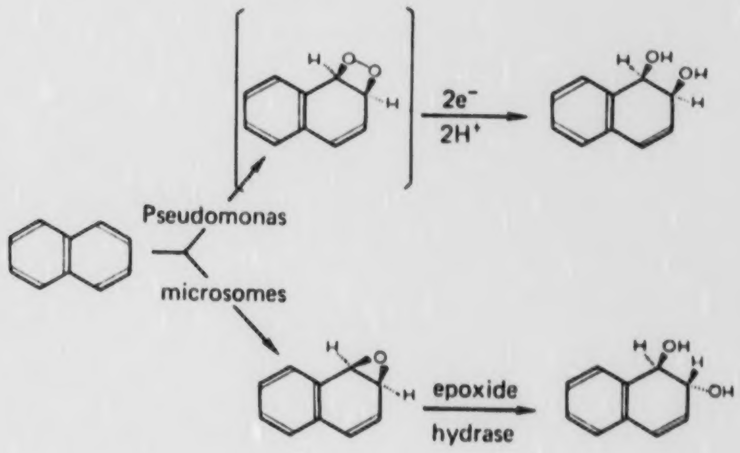


Figure 3. Proposed mechanisms of naphthalene dihydrodiol formation in mammalian and microbial systems [Gibson, 1972]

However, the highly chlorinated PCB's have been found to be stable to metabolism by either microbial (Sarofim and Nisbet, 1972) or mammalian systems (Hutzinger *et al.*, 1972). An intuitive correlation based on the similarity in structure between PCB's and chlorinated naphthalenes would suggest that the highly chlorinated naphthalenes might be quite stable in the environment.

Studies of the photochemical or chemical degradation of chlorinated naphthalenes have not been undertaken.

B. Environmental Transport

Since chlorinated naphthalenes have not been detected in the environment, no information is available on their transport within the biosphere. The similarity between the physical properties (low water solubility, low volatility) of chlorinated naphthalenes and PCB's, would suggest that the transport of chlorinated naphthalenes within the environment might be quite similar to PCB's.

C. Bioaccumulation

Studies of the behavior of chlorinated naphthalenes exposed to ecological food chains are not available. Again, the physical properties (water insoluble, soluble in organic solvents) may suggest a similar behavior for chlorinated naphthalenes to that found for PCB's.

X. Toxicity

A. Human Toxicity

Because chlorinated naphthalenes have never enjoyed widespread household use, occupational rather than accidental or environmental exposure predominates the relevant literature on human toxic effects. Two clinically distinct but often concurrent and possibly physiologically related syndromes have been described: liver necrosis and chloracne. Any attempt to label these syndromes as acute or chronic is potentially misleading. While an exposure of 3-4 months is often noted in the clinical literature (e.g. Schwartz and Peck, 1943; Collier, 1943; Greenburg, et al., 1939), histotoxic effects may appear after a much shorter period (Weil and Goldburg, 1962). Also, human susceptibility is by no means homogeneous. Standard clinical parameters such as age, sex, weight, general physical conditions, and previous medical history show no clear correlation to chloronaphthalene pathogenesis (Greenburg, et al., 1939). The situation is further complicated in that precise dosage values are often not available. But, if a label would be necessary, chronic is perhaps the best compromise with the disease appearing after an appreciable period of exposure and reversal being relatively gradual after exposure is discontinued. A more productive approach would probably be in terms of degree of damage as adopted by Collier (1943); i.e., slight, moderate, and severe.

Chloronaphthalene-induced liver necrosis has always been of low incidence, with the last fatal case in the surveyed literature being reported by Straus (1944). The symptomatic course of the disease is not unlike that of other forms of liver damage resulting in hepatitis with consequent jaundice, and may be accompanied by nausea, vomiting, loss of appetite, fatigue, fever, and/or acute abdominal pain (Kleinfeld, et al., 1972; Collier, 1943). Autopsies of fatally exposed workers have revealed severe yellow atrophy of the liver. Most researchers seem to agree that the liver is the only internal organ directly damaged by chlorinated naphthalenes (Collier, 1943; Straus, 1944; Kleinfeld, et al., 1972). Detailed descriptions of the pathology are available in the literature--especially Greenburg (1939). Understandably, very little detailed descriptions of liver damage are available for non-fatal exposures (Straus, 1944). Kleinfeld, et al. (1972) could find no evidence of liver damage in a recent outbreak of chloracne.

Agreement also exists with reference to route of entry. Opinion favors inhalation as the prime, if not the only, form of hepatopathogenic exposure (Kleinfeld, et al., 1972; Crow, 1970). The earlier investigations cited above by and large recognized the importance of inhalation but did not specifically rule out contact exposure. Experiments with other mammals support the hepatotoxic effect of inhalation over absorption and also indicate a possible danger from ingestion. The one accidental case of ingestion reported by Crow (1970), however, does not allow any sound conclusions to be drawn.

The primary hepatotoxic agents for man seem to be the penta- and hexachloronaphthalene (Amer. Ind. Hyg. Assoc., 1966). Current hygenic standards are 5 mg/m^3 for trichloronaphthalene and 0.5 mg/m^3 for pentachloronaphthalene. These standards seem well below the minimum toxic doses for man and animals.

In contrast to the low incidence of liver damage, chloracne resulting from exposure to chlorinated naphthalene is a common and persistent problem in manufacturing and use. Chlorinated naphthalene dermatitis was reported as early as 1918 (Jones, 1941) and remains a problem in spite of advances in industrial hygiene (Kleinfeld, 1972). Chloracne is a general term and describes the skin irritation that can be produced not only by chlorinated naphthalenes but also by other chlorinated compounds including diphenyls, benzenes, and phenols. Chloracne accompanied by itching, however, may be specific to the chlorinated naphthalenes. The skin lesion is morphologically similar in all cases and has been referred to as the chloracne cyst - sores 1 mm to 1 cm in diameter with an ill-defined central opening. These cysts are formed from necrotic material which is retained in the hair follicle or sebaceous gland and covered by a horny layer of skin causing a dark crusty appearance (Crow, 1970). Hair follicles swell into acne-type sores and the sebaceous glands degenerate. In the more severe cases, which are usually associated with advanced liver damage, these lesions may cover extensive areas of the body with pigmentation so dark as to make a caucasian appear negroid (Greenburg, et al., 1939).

Although chloracne can be caused by ingestion or inhalation, the most common route in man is cutaneous absorption (Crow, 1970). The lower chlorinated naphthalenes seem to be innocuous with respect to man. Mixtures of mono-/dichloronaphthalene and tri-/tetrachloronaphthalene at 500 mg/g solvent applied to the ear caused no response over a 30-day period. A mixture of penta-/hexachloronaphthalene under the same conditions did cause acne but hepta- and octachloronaphthalene did not (Shelly and Kligman, 1957). Even at concentrations as small as 30 mg/g, typical chloracne develops in 6 weeks with the application of penta-/hexachloronaphthalene (Hambrick, 1957).

B. Toxicity to Birds and Non-Human Mammals

Chlorinated naphthalene toxicity in birds and non-human mammals has been studied in attempts to better understand not only occupational hazards to man but also highly chlorinated naphthalene poisoning to cattle. The former investigations have been conducted primarily with controlled exposures of rats to known concentrations of the toxic substance in order to supplement available human clinical data. The latter investigations on cattle toxicity have concentrated primarily on a complete description of the syndrome and on attempts to induce a toxic response in other farm animals under closely monitored conditions. Cattle poisoning as described below usually involves a relatively high dose with rapid physical deterioration. Thus, it may be characterized as acute. Studies relating to occupational exposure, however, usually involve attempts to elicit a gradual response to a minimum dosage and may thus be characterized as chronic.

1. Acute and Subacute Toxicity

Highly chlorinated naphthalene poisoning, also referred to as bovine hyperkeratosis or X-disease, was of major economic concern in the United States during the 1940s and 1950s. Basically, the disease was caused by accidental ingestion of chlorinated naphthalenes from lubricants in machines used for making pelleting feed or from wood preservatives (Crow, 1970). The relation of chlorination to toxicity in accidental cattle poisoning seems to agree well with that of human toxicity in that the penta-/hexachloronaphthalenes are usually the toxic agents. However, octachloronaphthalene has been reported as having greater oral toxicity than hexachloronaphthalene in cattle (Amer. Indust. Hyg. Assoc., 1966). As with human exposure, detailed dosage data are often lacking due not only to uncertain concentrations but also to *ad libitum* exposure.

The pathological course of bovine hyperkeratosis has been described in considerable detail and needs only a cursory examination in this report (See Olson, 1969). As indicated previously (Sect. VIII, E), a primary effect of chloronaphthalene poisoning is to interfere with the biotransformation of carotene to vitamin A. Chronologically, this is one of the first effects of exposure and many of the subsequent symptoms - especially of the skin and horns - may be due to vitamin A deficiency in the blood plasma. Vitamin A depression is quickly followed by inflamation of the oral mucosa, weeping, excessive salivation, and irregular food consumption. As the disease progresses, gross physical effects may include a general thickening of the skin caused by over-development of the skin's horny layer with loss of hair (hyperkeratosis). The horns may show signs of degeneration or irregular growth. With continued exposure, the disease progresses through anemea, dehydration, loss of weight, fever, and death. Liver damage may be severe [The resemblance of this syndrome to severe chloronaphthalene intoxication in man is noted but no unequivocal comparisons can be made]. A combination of penta-/hexachloronaphthalene at a total dosage of 5.55 mg/kg body weight given orally over a five day period will cause a sharp drop in plasma vitamin A by the end of the third day and depressed plasma vitamin A for over thirty days. A single dose of hexachloronaphthalene at 11 mg/kg body weight has caused mortality within two weeks (Olson, 1969).

Other domestic animals prove much less susceptible to chloronaphthalene poisoning than do cattle. Swine show no toxic effects to hexachloronaphthalene at ten times the above lethal dosage for cattle. Marked vitamin A depression is noted in swine only with dosages of 154 mg/kg body weight and death does not occur until 198 mg/kg body weight doses are given. Pentachloronaphthalene applied to the skin at 60 mg/liter, (3 liters per day), six times a week for six weeks [180 mg/day for a total dose of 6.3 g] causes only mild hyperkeratosis. (Link _et_ _al_., 1958) Similar doses administered orally (176-200 mg/kg body weight over a 8-9 day period) causes only slight systemic effects and ataxia (Huber & Link, 1962). Although hyperkeratosis did not result from oral administration, lethal oral doses did result in moderate to severe liver damage ranging from yellow discoloration to swelling and hemorrhage. In non-fatal oral doses, depression of plasma vitamin A was reversible upon oral administration of vitamin A (Link _et_ _al_., 1958). Similar resistence has been noted in sheep but these studies were not reviewed in this preliminary phase (see Olson, 1969).

Excellent concentration/effect studies have been conducted using chickens and may possibly indicate an increased resistance to chloronaphthalene exposure over that shown by cattle. Exact comparisons are difficult, however, because feeding was _ad libitum_: given the erratic effect of chloronaphthalene on the appetite exact dosages cannot even be meaningfully approximated. A mixture of penta-/hexachloronaphthalene at concentrations of 5, 10, 20, 50, and 100 ppm (mg/kg feed) for 40 days, gives an LC_{50} of 20 ppm with an average decrease in weight of 51%. Even at 5 ppm, weight gain was reduced by 33% with a 6.5% mortality and the prognosis for prolonged feeding as terminal by marketing age. At 100 ppm, all of the broad breasted bronze chickens died within 33 days. It is interesting to note that females were appreciably less sensitive over all dosage ranges; however, insufficient data is given to rationally assess whatever significance, if any, this may have. Gross histologic examination revealed enlarged and darkened livers as the only histopathologic manifestation, reenforcing the specificity of action found in human exposures. Similar to human topical application, octachloronaphthalenes even at 125 ppm in feed caused no significant effect. [The investigators speculated without elaboration that this might reflect the high melting point and low solubility of octachloronaphthalene.] (Pudelkiewicz *et al.*, 1958).

More relevant from the standpoint of comparative toxicology, a different variety chicken, the New Hampshire chicken, was studied in a subsequent experiment and found to be appreciably more resistant to penta-/hexachloronaphthalene poisoning. The lethal dose for the broad breasted bronze chickens, 100 ppm, only prevented egg production in the New Hampshire. With cases of 4, 20, 100, 500 and 2500 ppm in feed over 35 days, 100% fatality was only achieved with the highest level (after a two week exposure period). A four fold increase in vitamin A markedly decreased the effect. Again, enlarged fibrous livers were the most common pathological finding. (Pudelkiewicz et al., 1959). Whether the increased resistance of New Hampshires over broad breasted bronzes represents a true subspecies variation or only reflects any of a host of other possible causes (e.g., times of year, ambient temperature, size or health of original specimens, etc.), it does serve to illustrate the many possible pitfalls of comparing toxicity studies on widely dissimilar animals.

2. Chronic Toxicity: Rats and Rabbits

The clinical history of occupational poisoning due to chloronaphthalenes has stimulated much of the work done on "chronic" exposure to non-human mammals. Copeous and detailed dosage/response data are available and a selective but representative sample is included in the following discussion. Because the toxic properties of the chlorinated naphthalenes vary considerably with the degree of chlorine subsitution, chronic toxicity will be discussed in terms of ascending levels of chlorination.

a) Mono- and Mono/Di- Combinations:

These compounds are commonly considered non-toxic. Topical application of mono/dichlorinated naphthalenes in the human ear at 500 mg/g solvent for 30 days is non-reactive (Shelly and Kligman, 1957). However, when applied to the much more sensitive rabbit ear for 5-7 days, α-chloronaphthalene produces mild reddening at 90 mg/g and severe reddening - but without decrease of sebaceous glands - at 570 mg/g (Hambrick, 1957). [Inhalation and ingestion experiments were not encountered in the literature surveyed.]

b) Dichloronaphthalenes:

When applied topically to the rabbit ear at about half the above stated concentrations for α-chloronaphthalene (45 mg/g and 290 mg/g), dichloronaphthalene produced the same effects over the same period. (Hambrick, 1957). When ingested in ad libitum feeding by the rat at 5 g/kg of feed for 15 days, liver weight was increased, growth impaired, and coat texture roughened. (Wagstaff, 1971). [No inhalation experiments were encountered.]

c) Tri- and Tri/Tetra- Combinations:

Topical application of trichloronaphthalenes to mice and rats (at an unspecified concentration) for 2 hr/day x 40-60 days produced no effect (Shakhovskaya, 1953). This is in agreement with a mixture of tri/tetrachloronaphthalenes applied to the human ear at 500 mg/g solvent for 30 days which also had no effect (Shelly and Kligman, 1957).

Feeding experiments of trichloronaphthalene with mice at 2.5 mg/mouse/day x 20 days produced no effect (Shakhnovskaya, 1953). However, at 300 mg/rat/day x 9-136 days (total dose of 2.7 g-41 g) a slight but progressive increase in fatty accumulation was evident (Bennett et al., 1938). Tri/tetrachloronaphthalene at 15 mg/kg body weight/day x 60 days has no effect in rabbits - total dose of .9 g/kg body weight (Greenburg et al., 1939).

Inhalation experiments yield similar results with rats. At 0.05-0.2 mg/l for 2 hrs/day x 20 days and 1.31 mg/m^3 for 16 hrs/day x 134 days no toxic signs develope (Shakhnovskaya, 1953, Bennett et al., 1938). But at 10.97 mg/m^3 for 16 hrs/day x 102 days slight liver discoloration is shown and 5% of the rats show increased fatty degeneration (Bennett, 1938).

d) Tetra/Penta- Combinations:

With the introduction of the five chlorine atom compound, the first cases of severe poisoning develop. Rats fed 50 mg/rat/day x 63 days - total doses of 3.12 g/rat - are fatally intoxicated, showing jaundice and fatty degeneration of the liver (Bennett, et al., 1938). Rabbits seem even more sensitive with fatal intoxication at 15 mg/kg body weight/day x 12-26 day - total dose of 18-390 mg/kg body weight (Greenburg et al., 1939). (No inhalation or topical experiments encountered.)

e) Penta and Penta/Hexa - Combinations:

i) Pentachloronaphthalene alone has received relatively little attention. Applied to swine's skin at 60 mg/liter x 3ℓ x 6 day/wk x 4 weeks - 180 mg/day, total exposure 43.2 gm - slight hyperkeratosis is produced (Link et al., 1958). When fed to rabbits at 15 mg/kg body weight/day x 12-26 days - total dose of 180-390 mg/kg body weight - the administration is fatal.

ii) Combinations of penta/hexachloronaphthalenes are among the most often sighted in human toxicity and have been studied in some detail in the non-human mammals.

Orally penta/hexachloronaphthalene has been found highly toxic to rabbits and rats. In rats, oral doses of 300 mg/rat/day were fatal in 33 days or less - maximum dose of .99 g/rat. The livers were markedly yellow and showed extreme signs of fatty degeneration. A dosage of 100 mg/rat/day had the same effect over a 55 day period - .55 g/rat total dose. Slower and less severe liver damage was noted with a dose of 62.5 mg/rat/day, but further details are not given (Bennett _et_ _al_., 1938). In rabbits, the lethal dose is 15 mg/kg body weight/day for 12-26 days - total doses of 180-390 mg/kg body weight - with similar toxic effects (Greenburg, 1939).

Inhalation studies with rats show a similar dosage/effect relationship. Exposures to 1.16 mg/m^3 x 16 hr. x 134 day and 1.44 mg/m^3 x 16 hrs/day x 52 days yields jaundice, enlarged yellow liver and 69% fatality (Bennett, _et_ _al_., 1938).

Applied to the skin of the rabbit ear, 30 mg/day x 5 days caused only mild dermatitis with follicular attenuation (Hambrick, 1957).

f) *Hexachloronaphthalene*:

Like pentachloronaphthalenes, hexachloronaphthalenes have received little attention. In *ad libitum* feeding to rats, 20 mg/kg and 63 mg/kg in diet causes weight loss over a 84 day period and 200 mg/kg diet causes fatality in unspecified numbers (Weil and Goldberg, 1962).

Skin exposure to the rabbit ear at 30 mg/g solvent for five days caused decrease in sebaceous gland tissue (Hambrick, 1957).

g) *Heptachloronaphthalene*:

No chronic studies in heptachloronaphthalene were encountered

h) *Octachloronaphthalene*:

The toxicity of octachloronaphthalene is somewhat problematical. Most current investigators consider it innocuous (Crow, 1970; Olson, 1969). No significant toxic effects have been observed after testing in man or chicken (Shelly & Kligman, 1957; Pudelkiewicz *et al*., 1958). However, *ad libitium* feeding of rats at dietary concentrations of .5 g, 2 g, and 5g/kg for 22 days has shown a decrease in liver but not plasma vitamin A (Deadrick *et al*., 1955). Further, a single dose of 1 g/rabbit caused fatality in 7 days (Cornish & Block, 1958).

3. *Sensitization*:

In the strictest sense of the word - i.e., an increased response to a toxic substance based on an antigen/antibody-type activity - sensitization does not seem to apply to the chloronaphthalenes. Further, there is no apparent evidence that any organism becomes increasingly reactive to chloronaphthalenes with exposure. This should not be confused with increased susceptibility to chloronaphthalenes because of previous liver damage.

4. Teratogenicity: No studies encountered.

5. Carcinogenicity: No studies encountered.

6. Mutagenicity: No studies encountered.

7. Behavior effects: No studies encountered.

C. Toxicity to Lower Animals

Because the problems encountered in the manufacture and use of chlorinated naphthalenes center on the "higher" animals, no toxicology data is available. However, it has been determined that α-chloronaphthalene does not effect the schooling behavior of the fish *Kuhbia sandvicensis* at 20 ppm. (Hiatt *et al.*, 1953).

D. Toxicity to Plants

No studies encountered.

E. Toxicity to Microorganisms

Very few studies have appeared in the literature in relation to microbiotic toxicity. Those few that have are in the foreign literature and relate primarily to the use of chloronaphthalenes as wood preservatives. Hexa- and octachloronaphthalenes were found to be non-toxic to spores of millet smut at unspecified concentrations and exposures (Mel'nikov *et al.*, 1958). Low but unspecified concentrations of unspecified chlorinated naphthalenes may stimulate cellulases in *Trichnymphia agilis*, a flagellated symbiont of the damp wood termite. This results in increased cell volume, but the toxicity - if any - is not discussed (Schulze-Dewitz, 1964).

XI. Chlorinated Naphthalenes: Summary and Conclusions

The chlorinated naphthalene industry has little apparent growth potential and may actually be on the wane. Over the past sixteen years, total production has decreased by 14%. The applications for chlorinated naphthalenes also seem to have become more restricted. The compounds are no longer used as wood preservatives, at least not in the United States and probably not in other countries. No proposals for new uses have been encountered. The reason for this decline is most probably attributable in part to the appreciable mammalian toxicity of the penta- and hexachlorocompounds. Production cost and the availability of alternative substances may also be factors. However, the five million pound production in 1972 is by no means negligible and environmental contamination is possible. A realistic determination of potential ecological hazard based on what is known can be made by an integrative evaluation of production, use, toxicity, environmental exposure, and persistence for the various groups of chlorinated naphthalenes.

Mixtures of mono- and dichlorinated naphthalenes (Halowaxes 1000 and 1031) represent about one quarter of the production. Their uses as engine oil additives and in the fabric industry may indicate more direct routes of environmental contamination to soil or water than found in the higher chlorinated naphthalenes. However, these compounds have thus far shown an extremely low order of toxicity and are likely to be readily decomposed in the environment.

Combinations of tri/tetra with some di- and pentachloronaphthalene (Halowax 1001 and Halowax 1099) form the bulk of the market (approximately 65%) and are used exclusively as impregnates for automobile capacitors. Although most of these capacitors must eventually be replaced and probably end up in land fills, the extent to which chlorinated naphthalenes will leach out of the closed system has not been determined. These compounds might present a serious hazard if leached into the environment in large enough amounts. Some tetra/penta combinations have been implicated in liver degeneration and hyperkeratosis at doses of 15-50 mg/kg body weight. Further, these compounds are likely to be relatively stable in the environment.

The tri- through hexachloronaphthalene based products (Halowaxes 1013 and 1014) are also likely to possess a high degree of toxicity and persistence. Although they represent only about 8% of the market, their uses as electroplating stopoff compounds and impregnates for carbon electrodes used in chlorine production would seem to indicate a marked increase in potential environmental exposure over that shown by capacitor impregnates.

The last commercial mixture, hepta-/octachloronaphthalene (Halowax 1051), is produced in rather small amounts and for purposes which were not ascertained. The toxicity data on these compounds are inconclusive. They are, however, likely to prove quite stable. Because of the lack of definitive information, a reliable assessment of potential environmental hazard cannot be made.

In summary, even the most toxic of the chlorinated naphthalenes may present little environmental hazard because of their limited production and restricted use. However, this type of conclusion could not be justified based on present information alone. Much that should be known about the chloronaphthalenes - their environmental fate, the actual degree and rate of contamination, and their toxicity to intermediate life forms - is all but unexplored. Thus, none of the chlorinated naphthalenes can be dismissed in a consideration of potential environmental hazards. The mono- and dichloronaphthalenes used in the oil and fabric industries may indeed have a low order of toxicity and be readily biodegraded but they represent a sizable portion of the market and are liable to direct environmental exposure. The chloronaphthalenes used in automobile capacitors (primarily tri- and tetra- compounds) warrent careful evaluation because of their high production, probable persistence, and demonstrated toxicity. Further, the possibility of leaching,although seemingly remote, cannot be disregarded. Similarly, the tri- through hexachloronaphthalenes used in electroplating and chlorine production, although produced in limited amounts, must be considered because of their stability, toxicity, and significant potential for environmental release. Finally, the hepta-/octachloronaphthalenes require further investigation in spite of their small production because little is known about the applications, potential release, and toxicity of these highly stable compounds.

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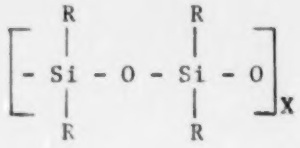
SILICONES
(SILOXANES)

I. Physical Properties

Silicones, or more chemically proper -- siloxanes, are compounds which contain a repeating silicon-oxygen backbone with organic groups attached to the silicon atoms. This inorganic Si - O - backbone provides some extremely unusual physical characteristics to these semiorganic compounds.



$$\left[- \overset{R}{\underset{R}{\mathrm{Si}}} - O - \overset{R}{\underset{R}{\mathrm{Si}}} - O \right]_x$$

In general, these physical properties can be characterized as high thermal and oxidative stability and inertness, low surface tension, low polarity (hydrophobicity), low viscosity for given molecular weight, high compressibility, high permeability to small molecules, and low surface energy (good release characteristics). In addition, the properties of silicones change less on going to either high or low temperatures than do those of most other materials. (Nolls, 1968; Meals, 1969; Lichtenwalner and Sprung, 1970; Hyde, 1965).

The following discussion will be divided into three sections: silicone fluids, silicone rubbers, and silicone resins. Commercially, these are quite separate categories. The physical properties of all the commercial products are quite dependent upon the R-group substitution. This will be further discussed under each section.

A. Silicone Fluids

The bulk of the technical silicone oils consists of dimethylsilicone oils with methylphenylsilicone oils being next most important. These compounds remain in the liquid phase over an unusually large range of molecular weights [MW = 162 (hexamethyldisiloxane) to MW ≈ 500,000] and provide a wide range of viscosities (0.65 to about 1,000,000 cSt.) (see Table I).

Table I

Physical Properties of Some Technical
Methylsilicone and Methylphenylsilicone Oils (Noll, 1968);
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ν_{20} °C (cSt)	Pour point (°C)	Flash point (°C)	Flame point (°C)	d_4^{20}	n_D^{20}
		Methylsilicone Oils			
60	< −60	> 300	> 350	0.96	1.4041
140	< −50	> 315	> 380	0.97	1.4045
440	< −50	> 315	> 380	0.97	1.4053
680	< −50	> 315	> 380	0.97	1.4053
1,440	< −50	> 320	> 390	0.97	1.4053
10,000	< −50	> 320	> 390	0.97	1.4058
50,000	< −50	> 320	> 390	0.97	1.4058
100,000	< −50	> 350	> 400	0.97	1.4058
300,000	< −40	> 350	> 400	0.97	1.4058
		Methylphenylsilicone Oils Low Phenyl Content			
200	~ −65	> 300	> 360	1.03	1.465
1000	~ −55	> 315	> 360	1.04	1.475
		High Phenyl Content			
300	~ −40	> 300	> 360	1.06	1.505
1000	~ −30	> 305	> 360	1.09	1.515
		Branched Methylphenylsilicone Oils			
5	~ −102[a]	130	160	0.92	1.436
10	~ −70[b]	145	175	0.98	1.493
25	~ −78[c]	170	200	0.99	1.457
75	~ −62[d]	210	260	1.01	1.469

[a] Boiling point is 105 °C/1 torr.
[b] Boiling point is 135 °C/1 torr.
[c] Boiling point is 175 °C/1 torr.
[d] Boiling point is 220 °C/1 torr.

The low variation of the viscosity of methylsilicone oils with temperature is one of their most striking properties (see Figure 1). As the methyl groups are replaced by other aliphatic or aromatic groups, the temperature dependence of the viscosity increases.

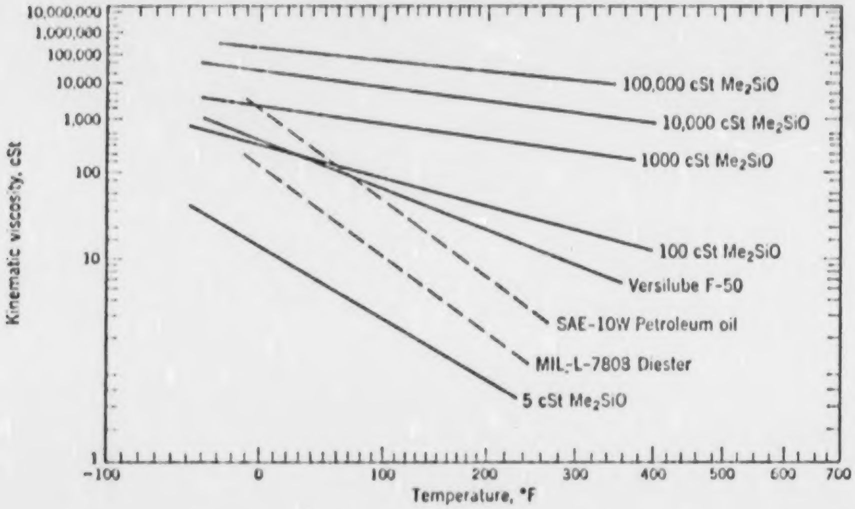

Figure 1

Viscosity-Temperature Curves for Various Silicones (Meals, 1969); reprinted by permission. Copyright 1969, J. Wiley and Sons

Methylsilicone and phenylmethylsilicone are soluble in a large number of different solvents. Good solvents include hydrocarbons, chlorinated hydrocarbons, ethers, esters, and alcohols containing four carbons or more. The solubility depends to some extent on viscosity, molecular weight, and constitution (Nolls, 1968).

Only the lowest members of the linear siloxane oils are distillable, although some branched low molecular weight polymers are used as diffusion pump oils because of their steep vapor pressure-temperature curves. Table II presents some vapor pressure measurements for the less volatile fluids.

Table II

Vapor Pressure of Silicone Fluids
(Nolls, 1968)

cSt (20°C)	Vapor Pressure (mmHg)
140 (dimethyl)	$<10^{-5}$ (140°C); 1×10^{-4} (170°C); 8×10^{-4} (200°C)
200 - 1000 (methylphenyl)	10^{-6} (20°C); 10^{-5} (100°C); 10^{-4} (150°C)
30,000 (methyl)	5×10^{-5} (100°C); 3×10^{-4} (220°C)

The surface tension of liquid silicones is surprisingly low. For the linear siloxanes it rises from 15.7 dynes/cm for hexamethyldisiloxane to about 20 dynes/cm and then remains constant as the viscosity increases. The surface tension increases as the content of phenyl groups increases.

The dielectric properties are characterized as good in terms of dielectric constant, loss factor, specific resistance and dielectric strength and vary only slightly with temperature.

The lubricating properties of silicone oils are generally poor. The load-bearing properties of the methyl siloxane films are low because of the weak intermolecular forces. Improved lubricating properties are obtained by incorporation of phenyl groups (especially substituted phenyl groups, e.g. chlorophenyl) and long chain alkyl groups.

B. Silicone Rubbers

The type of substitution of the silicone atom is not the only determinant in silicone rubber properties; other parameters include the processing technique and the method and type of vulcanization. However, in general, the silicone rubbers can be characterized as having high heat resistance (to dry air), low-temperature flexibility, resistance to ozone and weather, superior mechanical properties at high or low temperatures, high permeability to gases and liquids, excellent release properties (even from adhesive materials such as tar, rubber mixtures, resin, and asphalt), and good electrical properties, especially at elevated temperatures.

C. Silicone Resins

The properties of silicone resins make these polymers important to both the paint and electrical industries. In the paint industry the mechanical properties of hardness, elasticity and thermoplasticity (heat resistance) are most important. The film hardness of the pure silicone resins is generally too low and the thermoplasticity too high for the paint industry. Therefore, cocondensations of silicones and polyesters are preferred. Silicone resins also exhibit high weather resistance.

The electrical industry uses silicone resins because of their heat resistance and good electrical properties in terms of loss factor, dielectric constant, and specific resistance.

II. Production

In the United States there are four major producers of silicones: Dow Corning Corporation, General Electric Company, Stauffer Chemical Company and Union Carbide Corporation. Dow Corning, the largest producer (approximately ½ of total production), manufactures silicone fluids, resins, and elastomers at Midland, Michigan and has a dimethyl silicones plant at Carrollton, Kentucky. Silicone products are also produced at Elizabethtown, Kentucky (silicone sealants), Hemlock, Michigan (medical grade silicones) and Trumbull, Connecticut (rubber compounds). The Silicone Products Department of GE makes silicone fluids, resins and elastomers at Waterford, New York and silicone resin based products at Coshocton, Ohio. The Silicones Division of Union Carbide produces silicone fluids, resins and elastomers at Sistersville, West Virginia. The Silicone Division of Stauffer, the smallest producer (approximately 5% of the market), produces silicone fluids and elastomers at Adrian, Michigan and elastomers at Matawan, New Jersey. (Lewis, 1967).

Details on plant capacities are not available and total production figures lack precision due to the fact that many manufacturers fail to differentiate between finished products, which contain water or solvent, and 100% silicone material. An estimate for 1965 placed the total production of silicones (fluids and silicone content of resins and elastomers) at about 1.13×10^{10} gms (25 million lbs) (Anon., 1965). Table III provides production levels for silicone resins and elastomers which were published by the U.S. Tariff Commission (1951-1971). It is unclear

Table III

Production of Silicone Resins and Elastomers
(U.S. Tariff Commission 1951-1971)

	Resins		Elastomers	
	(10^9 g/yr)	(10^6 lb/yr)	(10^9 g/yr)	(10^6 lb/yr)
1951	0.59	1.3	---	---
1952	0.77	1.7	---	---
1953	1.18	2.6	---	---
1954	0.86	1.9	1.00	2.2
1955	1.36	3.0	---	---
1956	1.59	3.5	---	---
1957	1.54	3.4	---	---
1958	1.41	3.1	---	---
1959	2.27	5.0	2.36	5.2
1960	2.31	5.1	2.22	4.9
1961	3.54	7.8	2.59	5.7
1962	3.86	8.5	3.04	6.7
1963	4.49	9.9	3.72	8.2
1964	4.99	11.0	3.76	8.3
1965	---	---	4.94	10.9
1966	4.08	9.0	6.03	13.3
1967	---	---	4.31	9.5
1968	---	---	4.17	9.2
1969	---	---	6.12	13.5
1970	---	---	5.58	12.3
1971	7.62	16.8	7.53	16.6

how these reported figures relate to 100% silicone material (e.g. silicone-alkyd resins contain as little as 15% silicones). Union Carbide (Bailey, 1973) has suggested that the total market (including water in silicone emulsions and solvents in resin solutions) is approximately 91 - 136 x 10^9 g (200 - 300 million lbs.). The Dow Corning Corporation (1973) has estimated the U.S. market for 1973 to be approximately 41.3 x 10^9 g (91 million lbs.) consisting of the product categories depicted in Table IV.

Table IV

Estimated Silicone* Usage in U.S. Market - 1973
(Dow Corning Corporation, 1973)

	10^9 g	10^6 lbs	% of total
Methyl Siloxanes (fluids (~50% of total), compounds, rubber, sealants)			
Dimethyl siloxanes	13.61	30	33
Methyl and small quantities of phenyl, vinyl, chlorophenyl, etc.	13.61	30	33
Silicone Glycols (used with polyurethanes)	8.16	18*	20
Chemicals	1.36	3	3
Miscellaneous (resins, resin intermediates fluorosilicones)	4.54	10	11
Total	41.28	91	100

*Represents silicone content except for silicone glycols. Approximately 30% of the silicone glycol figure represents siloxane compound.

III. Uses

Silicone fluids, rubbers and resins are used in an incredible number of diverse applications in industrial processing and products, consumer products, and biomedical uses (Thimineur, 1972; Ames, 1958). The fluids have the most commercial uses with dimethyl and phenylmethyl fluids being the most important. It has been estimated that 45% of the total silicone production goes into silicone fluids, 30% into rubbers, and 10% into resins, with the remainder probably made up of silicone coupling agents (Lewis, 1967)

A. Silicone Fluids

Although the major technical interest in silicone fluids is due to their thermal stability, electrical properties and viscosity/temperature characteristics, the commercial utilizations have been based on their water-repellency, low surface tension, and release properties. This is undoubtedly due to the high cost of silicones which disallows their use in bulk quantities (the former properties) except in unusual circumstances. The commercial utilization of the surface properties of silicones is discussed in the following paragraphs.

1. Waxes and Polishes

Most furniture, car and gloss waxes and polishes contain silicone fluids. They reduce the work required to spread the polish and they improve the gloss. The silicone content in most polishes varies from 2 - 5%, while pastes contain somewhat higher silicone content.

2. Cosmetics

The physiological inertness, lubricative properties and water repellent properties of silicone fluids have allowed their use in cosmetic preparations. These uses have included hand creams and lotions, hair sprays, preshave lotions, after-shave lotions, shaving creams, suntan preparations, lipsticks, toothpastes, and deodorants.

3. Urethane Foams

A major use for silicone fluids is in a silicone-polyether copolymer fluid (silicone glycols) for use in one shot polyurethane foam, where they act to give control of pore size and to guide toward closed- or open-cell types of foam. Other uses for the copolymer fluids include additives in cosmetics and paints and use as release agents (Thimineur, 1972). Dow Corning Corporation (1973) has estimated the 1973 U.S. market of silicone glycols at 8.16×10^9 g (18 million lbs.).

4. Silicone Greases

By combining grinding fillers and other materials with silicone fluids, silicone greases are made. These are generally employed where high temperatures would destroy petroleum or vegetable oil.

5. Silicone Emulsions

Silicone fluids formulated into emulsions are used in a large number of industries as abherents (release agents) and as antifoam agents. The emulsions are sprayed on molds in very small quantities to allow the release of shaped material in such industries as the metal processing industry (die casting and shell-molding), food industry, rubber processing industry, paper coating and pressure-sensitive tapes industry (Bey, 1972), and the glass industry (Kovach, 1963).

Silicone emulsions used as antifoaming agents can be used in remarkably small amounts (0.0001 to 0.02% of material to be de-foamed). They find use in a wide variety of processing applications including petroleum refining, coatings, textile finishing, latex processing, food processing, and many more (Thimineur, 1972).

Silicone emulsions are also used in sizable quantities to impart stain and water repellency to textile products, especially wash and wear items. In addition, the textile industry uses the emulsions as fiber and thread lubricants, softeners with durable press resins and latex coatings, and as a low concentration additive in textile coatings to eliminate tack and blocking (Blumenstein, 1968).

6. Other

Besides being used in cosmetic preparations, silicones are also used in such household and consumer products as aerosol starch, domestic oven treatment, textile and leather treatments, treatment for ignition systems, rubber lubricants, artificial snow, and ironing aids.

Although the dimethyl and methylphenyl silicones do not provide good lubricity properties, addition of long chain alkyl groups or halogenated phenyl groups to the siloxane polymer chain imparts very good lubricating properties and, therefore, small amounts of these compounds find use as lubricants.

Other miscellaneous applications include defoaming agents in pesticide formulations; damping of dashpots, aircraft instruments, gyros, and meters; use in torsional vibration damping devices; use as dielectric fluids in transformers and capacitors; and use as baths in the treatment of burns, lubricants for artificial eyes, use for gastric disorders, and use for storage of antibiotics.

7. New Applications

Considerable study of dimethyl silicone fluids as brake fluids in automobiles has been undertaken. In addition, the possibility of using fluids as an antitranspirant for plants to reduce the lost of water in dry areas is being considered. In general, it is anticipated that silicone fluids will be replacing other chemicals in uses that provide human exposure or release to the environment when the physical properties of the silicones are appropriate. The major reason anticipated for this shift is the relatively low toxicity of the dimethylpolysiloxanes.

B. Silicone Rubbers (Elastomers)

Siloxane rubbers can be divided into two categories: (1) heat vulcanized and (2) room temperature vulcanized (RTV). In 1967 the heat vulcanized rubber comprised by far the largest part of the market (Lewis, 1967). Both these types of rubbers find application because of their outstanding resistance to both high and low temperatures. Their electrical uses include applications in insulation of wire and cable, coating of glass cloth, or other fabric for insulation, spark-plug boots, insulation for ignition harness in automobiles, and potting, encapsulating, and embedding electrical and elctronic devices, circuits or systems. Other uses include O-rings, gaskets, and aerodynamic seals (e.g., seals for aircraft doors) and molds for casting epoxy coatings of transistors (RTV). In the construction industry the RTV rubbers are used to seal spaces between masonry, and between masonry and windows, as well as to surface roofs and to seal glass into window-wall construction. In the biomedical field rubber parts are used for surgical tubing, for heart valves, for prosthetic parts and contact lenses and RTV rubber is used to encase "pacemakers" for heart patients. Silicone rubbers have a decided advantage for medical uses over other materials because they seldom contain materials such as plasticizers which may be leached out. RTV rubber is also used in adhesive and sealant consumer products (e.g., caulking around bathtubs and repairing dishes or plastic parts). Dow Corning also makes small quantities of fluorosilicone rubber to be employed where resistance to fuels, oils, and solvents is important. The silicone rubber market estimates for 1964 are presented in Table V.

Table V

Silicone Rubber Usage by Market: 1964
(Lewis, 1967)

Market	Percentage
Aircraft and missile	39%
Electronics	18
Electrical	14
Appliances	12
Automotive	6
Government (direct)	6
Miscellaneous	5
	100%

C. Silicone Resins

Silicone resins are particularly valuable to the electrical industry because of their high temperature resistance. The earliest use of silicone resins was for coatings in motors, generators, and transformers. They are also used to coat or impregnate glass cloth, mica paper, asbestos paper, and similar materials for electrical insulation.

Silicone resins also find applications in paints, water repellents, and release coatings. In paints they are usually blended with other resins (e.g., alkyd resins) to impart improved weather durability, heat resistance, and gloss retention (Hedlund, 1959). However, the increased cost has limited consumer use. In 1962 approximately one million pounds of silicone resins were reportedly used to treat masonry walls and highways to make them water repellent (Lewis, 1967). Another use for silicone resins is to treat paper to be used for covering adhesive surfaces such as "contact paper", adhesive tapes, and photographic film, and for packaging sticky foodstuffs. Table VI shows a market breakdown for silicone resins in 1962.

Table VI

Consumption of Silicone Resins (1962)
(Lewis, 1967)

Use	Percentage of the Market
Electrical Insulation	
Coating and bonding	31.3%
Impregnating	12.5
Laminating	12.5
Paint	18.7
Water Repellents	12.5
Release Coatings	9.4
Molding	3.1
	100.0

IV. Current Practice

Since silicones are quite stable at ambient temperatures and relatively physiologically inert, they present little problem during transport and handling. Most shipments are sent in 55 gal. drums, although some tank car shipments are used for intercompany transport or for large consumers. In most cases no special DOT label is required and when it is, it is usually due to the solvent used.

Correspondence with some of the manufacturers suggests that waste materials are either incinerated or landfilled. Water effluents are clarified and settled before release.

V. Environmental Contamination

No published information is available on environmental contamination from the use, production or disposal of silicones. Several of the known uses of silicone would suggest that they are released into the environment; for example, defoamers in water systems and pesticides, and car polishes. The proposed use of dimethylpolysiloxanes as plant antitranspirants would also indicate a high potential for environmental exposure.

Contamination from silicone production is being studied now by A.D. Little, Inc. under an EPA contract. The final report is scheduled for the middle of November, 1973. Union Carbide (Bailey, 1973) has stated that occasionally a small oil slick is observed in the water effluents from its Sistersville plant, but that the problem has been largely eliminated by water clarifiers and settlers. They suggest that the only significant source of silicones in the environment is from landfilling solid silicone residues and sludges.

VI. Monitoring and Analysis

Although analytical methods for monitoring environmental samples of silicones have not been reported in the surveyed literature, a number of methods have been developed for detecting silicones in the ppm range in food and beverage samples. This is undoubtedly due to the recommended limit of 10 ppm in foodstuffs.

Horner, et al. (1960) reported both a specific and non-specific method for detecting trace amounts of silicones in foods and biological material. The nonspecific method consisted of a colorimetric silica analysis of silicones in foods digested with fuming sulfuric and nitric acids. Jankowiak and LeVier (1971) later modified this procedure in order to eliminate phosphorus interferences. This method is best applicable to samples which contain negligible amounts of residual silica. The high level of silicon occurrences in nature precludes the use of such nonspecific methods for detecting silicones. The specific method used was a selective extraction of silicone with infrared quantification (7.95 μ band). The method was utilized in the 2 to 20 ppm range in pineapple juice. Sinclair and Hallam (1971) have used a similar technique to determine dimethylpolysiloxane in the 0.2 to 2.00 ppm range in beer and yeast. A low temperature specific extraction of siloxanes from fatty foods with quantification by atomic absorption (nonspecific but more sensitive than IR) or UV spectrometry has been reported by Neal, et. al. (1969).

The Dow Corning Corporation (1973) has reported that it uses an extraction procedure to determine low levels of silicones in soil and water. The preferred solvent is methyl isobutyl ketone (MIBK) which can be used directly for the atomic absorption quantification of silicon. Preliminary investigations show this method to be sensitive at the ppb range for water samples. No actual monitoring data is available yet.

VII. Chemical Reactivity

The commercial polysiloxanes are chemically quite stable and inert at ambient temperatures and neutral conditions. The SiO bond is about 50% ionic, with silicon the positive member (Meals, 1969), and this causes siloxanes to be quite susceptible to heterolytic cleavage, ie., to attack by acids or basis. However, at neutral pH hardly any hydrolysis takes place. Fox et al., (1950) have suggested that "appreciable" hydrolysis may take place when a large interface exists between water and silicone. The relative rate of such a process is unknown. The siloxanes are also stable at normal temperatures to air, oxygen, metals, wood, paper, plastics, and also to solutions of metal salts, liquid ammonia, and 3% hydrogen peroxide. They will react, especially at elevated temperatures, with strong mineral acids, particularly hydrofluoric acid, alkalis, and strong oxidizing agents such as concentrated nitric acid or elementary chlorine (Nolls, 1968).

Exposure of silicone polymers to light has a tendency to cause cross linking of the polymer. For example, Delmar et al., (1969) found that exposure of a methylsiloxane resin to a xenon arc lamp (>281 mμ) resulted in an increase of Si-CH_2-Si linkages.

Several authors have reported studies on the thermal and oxidative stability of silicones. Scala and Hickam (1958) found that phenyl substituted silicones offer greater resistance to degradation than the methyl-

and vinyl-substituted silicones and noted that DC 200 (dimethylpolysiloxane) gelled to a solid state in 3 hours at 250°C. Thomas and Kendrick (1970) in a thermalgravimetric investigation in vacuum concluded that the activation energy of depolymerization is mainly a function of the inductive effect of the substituent group (withdrawing groups increase the activation energy).

No correlation between these chemical reactions and biological processes has been drawn. However, in actual fact, their chemical inertness is similar to their apparent biological inactivity.

VIII. Biology

A. Absorption

As a rule, long chain polymers are less likely to be absorbed through the skin than the component monomers (Bischoff, 1972). Although there is insufficient experimental evidence for absolute conclusions, silicones seem to cross membranous surfaces only with difficulty and do not seem to be readily absorbed through skin surfaces (Hine _et al._, 1969). This may in part account for the inability of hexamethyldisiloxane to irritate rabbit skin even though the same compound does produce irritation when applied subcutaneously (Rowe _et al._, 1948). Similarly, Bennett (1973) indicates that polydimethylsiloxane fluids of six polymer units or less are absorbed orally but higher molecular weight compounds are not. Other routes of entry will be discussed in the appropriate areas under toxicity studies.

B. Excretion

Silicones injected spinally are not excreted in the feces or the urine (Hine et al., 1969). Excretion data was not given in other experiments screened. However, the laxative effect noted with oral administration would lead one to suspect that the silicones are eliminated in the feces (Rowe et al., 1948). Also, in that ^{14}C labeled dimethylpolysiloxane was found to be present but not accumulated in Bluegill Sunfish after a 30 day exposure period to

1 and 10 mg/l (Hobbs, 1973), an excretory mechanism can be postulated. This is consistent with the excretion of lower molecular weight dimethylpolysiloxanes noted by Bennett (1973).

C. Transport and Distribution

The distribution of silicones in the body and the transport mechanisms involved in distribution are highly dependent upon the route of administration. Intraperitoneal injection results in high silicone concentrations in the liver, gastrointestinal tract, and fatty tissue (Hine *et al.*, 1969). After intraperitoneal injection, the extent of fatty tissue distribution is likely to be dependent on the partition coefficients of the silicone polymeric species present (Bennett, 1973). In contrast to the intraperitoneal route, intracisternal injection results in high concentrations in the brain and vertebral column [see Tables VII and VIII].

Table VII

Distribution of ^{14}C-Labeled Silicone in Rat Tissues 25 Days after Intraperitoneal Injection of 15 μCi per Rat (Hine *et al.*, 1969)

Tissue	Rat number			Average percent activity/organ[a]
	1	2	3	
Fat	--	59.00	43.00	51.00
Heart	0.00	0.00	0.00	0.00
Kidney	--	0.74	0.51	0.63
Liver	--	16.1	13.5	14.80
Lung	0.08	0.05	0.08	0.07
Muscle	1.50	0.82	0.79	0.10
Skin	0.08	0.10	0.097	0.09
Brain	0.03	--	0.05	0.04
Spleen	2.80	0.17	0.30	1.56
Testes	--	1.70	0.12	0.98
Whole blood	0.00	0.00	0.00	0.00
Gastrointestinal	--	16.80	37.70	27.25

[a] Percent activity based on total counts received.

Table VIII

Distribution of ^{14}C-Labeled Silicone in Rat Tissues 45 Days after Intracisternal Injection of 6 μCi per Rat (Hine *et al.*, 1969)

Tissue	Rat number				Average percent activity/organ[a]
	1	2	3	4	
Fat	5.0	6.1	10.0	10.3	7.9
Brain	38.9	43.4	40.0	42.0	41.1
Vertebral column	33.9	32.0	27.9	32.0	31.4
Spinal cord	8.5	12.6	6.5	12.0	9.9
Spleen	0.09	0.58	0.0	0.16	0.21
Lungs	0.36	0.04	0.06	0.20	0.16
Liver	1.78	2.96	0.0	0.0	1.19
Gastrointestinal tract	0.0	0.0	0.0	0.0	0.0
Whole blood	0.0	0.0	0.0	0.0	0.0

[a] Average of 4 animals.

This type of route dependent distribution does not necessarily reflect passive transport mechanisms. When dimethylpolysiloxanes (350 and 1000 cSt.) are injected intra-articularly - i.e. into the knee joint of the male rabbit - the silicone fluid is gradually removed. However, the rate of loss does not vary with the degree of joint immobilization, thus suggesting an active distribution mechanism (Donahue, et al., 1971). Artificially induced blood transport has been examined by I.V. injections but to what extent this mechanism is used naturally is not clear (Reed and Kittle, 1959). The commonly noticed distribution of silicones in the kidney and liver might be explained in terms of filtration of silicones from the blood but further experimentation is necessary (Nosanchuck, 1968; Cutting, 1952). Because of the general impermiability of membrane systems to siloxanes, phagocytosis by wandering cells may also be a prime method of transport (Hine et al., 1969; Bennett, 1973).

IX. Environmental Transport and Fate

A. Persistence and/or Degradation

Under environmental conditions silicones are chemically quite stable (resistent to hydrolysis and oxidation) (see section on Chemical Reactivity). The same appears to be true for biological stability. Olson _et al._, (1962) reported that coating of cotton with silicone fluids made the textile more resistant to biodeterioration. Similar results were obtained by Hueck (1960) with silicone coated plastics and by Glazer (1954) with varnish compositions containing polydimethylsiloxanes. On the other hand, Zharikova _et al._, (1971) found that soil bacteria caused deterioration of organosilicon resin coatings and Inove (1973) found that molds were grown on silicone resins. Greathouse _et al._, (1951) and Caldron and Staffeldt (1965) reported that resins and rubbers made from the fluids were resistant to biodeterioration by a variety of soil microorganisms; although the latter observed that soil fungi were able to colonize on the rubber. Similarly, Ross (1963) found that silicone rubber-potted firing modules were very susceptible to fungus growth. In contrast, Muraoka (1966) noted that silicone rubber was resistant to deep sea microorganisms. The confusion in the results may be due to a lack of distinction between providing a surface for microbial growth and providing a nutrient source for the microbes.

Dow Corning has evaluated the effect of polydimethylsiloxane fluids of varying viscosities on the growth of bacterial species. The fluids were non-toxic, but the organisms could not grow without an exogenous nutrient. Examination of the fluids (20 cSt and 100 cSt) showed no alteration in the molecular distribution of the fluid components following the growth of organism (E. coli and S. aureus) (Bennett, 1973).

Both Union Carbide and Dow Corning have run biodegradability tests on silicone fluids. Union Carbide (Waggy, 1971) determined the stability of a silicone fluid (50 cSt) (330 ppm) and a silicone glycol fluid (660 ppm - 1000 ppm) (used for foaming polyurethane) with a Warburg respirometer system and dilution bottle BOD procedure (silicone glyconol only). These compounds were found to be completely nonbiodegradable.

Dow Corning (1973) ran a 70 day aerobic biodegradability test on ^{14}C labelled dimethylpolysiloxane exposed to sewage microorganisms. No biodegradability was noted under the experimental conditions.

B. Environmental Transport

Little information is known about the transport of silicones through the environment mainly because of the lack of monitoring data. Dow Corning (1973) has conducted some preliminary studies on leaching properties in soil. With damp soil they have concluded that silicones are fairly mobile. The vapor pressure of silicone fluids (10^{-5}-10^{-6} mmHg) is similar to PCB's (10^{-4}-10^{-6} mmHg) and DDT's (10^{-5}-10^{-7} mmHg), and, therefore, atmospheric transport may be an important environmental route.

C. Bioaccumulation

Although bioaccumulation studies of silicones in low trophic levels of the food chain have not been reported, some study with fish has been undertaken by Dow Corning (Hobbs, 1973). Bluegill sunfish were exposed to ^{14}C labelled polydimethylsiloxane for 30 days at 1 and 10 ppm. No evidence of accumulation was observed and the tissue storage in these fish was minimal.

X. Silicone Toxicity

A. Human Toxicity

1. Occupational Exposure:

Although certain chemical intermediates and silane monomers used in the preparation of silicone polymers do have considerable toxic potential, silicone polymers themselves are not reported to represent an occupational hazard (Hobbs, 1973; Bailey, 1973; Taylor, 1950). Absolutely no concrete data or observations were found in the literature surveyed to contradict or in any way dispute these reports.

2. Liquid Injection of Silicones:

Liquid silicones have been injected into the human body for various medical procedures, most involving some form of cosmetic therapy of which mammaplasty has stimulated the most controversy. Mammaplasty, the enlargement of the female breast by the injection of a fluid, has been accomplished most often using dimethylpolysiloxanes (viscosity of 350 cSt.) or a combination of this silicone with various organic fluids (Bischoff, 1972). In the late 1960's, various and often severe adverse reactions from this procedure were noted, ranging from mastitis to loss of the treated glands (Chaplin, 1969; Symmers, 1968). Although similar but less severe complications had been noted before this time, the primary cause was often attributed to the various additives rather than the silicone itself, with manufacturer's investigations showing no severe response to the purified silicone (Berger, 1966). This conclusion would seem within reason: In a case sighted in which both breasts were lost, an acute allergic response was noted (Chaplin, 1969), whereas the purified silicone has not been shown to produce an allergic response at least in rats (Nosanchuk, 1968). Even now that silicone mammaplasty has been prohibited in the United States, the culpability cannot be placed clearly (Bischoff, 1972).

3. Toleration by the Human Eye:

DC 360 Medical Fluid (2000 cSt.) has been injected into the eye as therapy for retinal detachments. This condition involves separation of the retina from the choroid membrane. Although this type of therapy has evolved no clear cases of adverse effect, a growing concern over possible long term damage has stimulated detailed investigations on non-human mammal systems and some controversy (Lee _et_ _al_., 1969; Mukai _et_ _al_., 1972). A recent unpublished investigation reported by Labelle and Okun (1972) indicates a clinically satisfactory ocular tolerance to DC 360.

4. Degeneration of Silicone Heart Valves:

Degeneration of silicone rubber heart valves has been one of the major problems in the application of silicone to humans (Bischoff, 1972). Recently, an attempt has been made to demonstrate that this problem is due primarily to silicone absorption of polyunsaturated fatty acids and their subsequent oxidation

by molecular oxygen. This mechanism has been proposed to account for the up to 15% increase in weight found in some defective valves (Carmen and Mutha, 1972). While this may serve as a satisfactory explanation for some cases of valve failure, it does not seem to account for all the clinical data. In a study by Roberts and Morrow (1968), 11 of 12 patients died after a post-operation period of two years or more. Of these, only five showed swollen valves. Six had silicone ball atrophy. Although no detailed data on valve weights are given, it seems unlikely that all of these cases could be accounted for in terms of lipid absorption. Recently, it has been reported that improved curing methods may overcome this problem (Anonymous, 1973).
The main significance of these findings is to indicate that silicone polymers may not be as unreactive in biological systems as once assumed (Bischoff, 1972).

5. Adverse Responses to Other Medical Silicones:

Similar reactions of other types of prosthetic devices were not reviewed for this preliminary survey. However, to underscore the human applications of silicones, some of the further uses and reactions cited by Bischoff (1972) are briefly summarized. Adverse responses have been noted in structural support devices of silicone applied to the human ear. Silicone lubricants in joints have shown no toxic reactions but do not appear to be of any benefit. Further, silicone antifoaming agents are reported to cause emboli in the capillaries of the heart, brain, and kidney, after intravenous injection.

6. Human Ingestion:

Silicones are not uncommon in the food industry both as additives and packaging materials and may reach the consumer in dietary doses of up to 10 ppm in most foods and up to 16 ppm in gelatin desserts (F.D.A., 1972). To date, however, no adverse effects of dietary consumption in the general population has been encountered in the literature. However, Bischoff (1972) references an article noting that hospital patients ingesting routine dietary silicones showed a decrease in the effectiveness of anticoagulation drugs. Other cases of drug interference or synergism have not been encountered and the relevence of this isolated occurrence is difficult to assess.

B. Toxicity to Birds and Non-human Mammals

1. Acute and Subacute Toxicity:

Adopting an entirely arbitrary distinction implied in the literature, acute and subacute toxicity will be used to specify toxic manifestations elicited in less than four months (see MacDonald *et al.*, 1960; Child *et al.*, 1951). Given this division, acute and subacute toxicity studies encompass a wide scope of diverse experiments. Thus, for the sake of clarity rather than classification, the literature will be discussed by the following routes of administration:

i) Ingestion
ii) Injection, I.M., I.V., Sub Cu., Intra-articular
iii) Intravitreal Injection
iv) Inhalation and Dermal Absorption

i) The "acute" feeding experiments generally indicate a low degree of silicone toxicity. D.C. 200 fluids have been examined for both single and multiple dose toxicity. By single administration to rats, only absurdly massive doses gave any toxic response [see Table IX].

Table IX

Mortality and Response Resulting from the Administration of Silicone Fluids in Single Oral Dose --Guinea Pigs

(Rowe et al., 1948)

Silicone	Viscosity in Cstks. at 25°C	Dose	Mortality Ratio	Observations on the Laxative Effects at Various Periods of Time after Administration			
				2½ hrs.	8 hrs.	24 hrs.	48 hrs.
		ml./kg.					
DC 200 Fluid (Hexamethyldisiloxane)	0.65	3.0	0/7				
		10.0	0/7	-	-	-	-
		30.0	0/7	-	-	-	-
		50.0	1/10				
DC 200 Fluid (Dodecamethylpentasiloxane)	2.0	10.0	0/3	-	+	-	
		30.0	0/6	-	++	-	-
		50.0	3/3				
DC 200 Fluid	50	10.0	0/2	+++	+++	+++	+
		30.0	0/6	+++	+++	+++	+++
		50.0	0/3				
DC 550 Fluid	75	3.0	0/3				
		10.0	0/3	+	+	+	
		30.0	0/6		++	+++	+++
DC 702 Fluid	35	3.0	0/3				
		10.0	0/3	+	++	+++	
		30.0	0/6		++	+++	++
DC 200 Fluid	350	5.0	0/2	-	-	+	
		10.0	0/5	-	+	+	-
		30.0	0/6	-	+	+	-
		50.0	0/3	-	-	++	++
DC 200 Fluid	12,500		Could not be fed satisfactorily				
Mineral Oil U.S.P.		10.0	0/2	++	++	+++	+
		30.0	0/3	+++	+++	+++	+

The fatalities caused by dodecamethylpentasiloxane and the central nervous system depression caused by hexamethyldisiloxane possibly may be attributed at least in part both to physical aggravation of the alimentary canal by large volumes of a foreign substance and to trauma caused by dosage administration. Repeated dosage administration to rats at 1 g - 20 g/kg body weight x 28 days revealed no toxic effects in growth, hematology, bone marrow, organ weights, or histopathology (Rowe et al., 1948). A similar experiment using DC 200 (350 cSt.) on rats and rabbits at 10g/kg feed plus 0.8% cholesterol x 84-119 days in _ad libitum_ feeding did produce renal tubular damage in rabbits but not in rats (Cutting, 1952). Negative results for rats were also found with G.E. Dri-Film No. 9977 - a dimethylsiloxane - at concentrations up to 20g/kg in feed _ad libitum_ over a 13 week period (Kern _et al._, 1949). A series of five dimethylpolysiloxanes (viscosities of 50 - 60,000 cSt.) also were reported to exhibit no toxic characteristics when fed to rats at concentrations of 10g/kg feed _ad libitum_ for 90 days (Mac Donald _et al._, 1960). A similar pattern is seen in studies on DC Antifoam A. Both Rowe and coworkers (1948) and Cutting (1952) found this compound to be non-toxic to rats in oral doses of up to 10 g/kg fed for 90-120 days. Rabbits, however, showed cellular infiltrations in the liver and kidney at concentration of 250 mg/kg DC Antifoam A and 0.8% cholesterol in feed (Cutting, 1952). The histologic damage in rabbits attributed to siloxanes by Cutting (1952) is disputed by subsequent investigators. Using an unaltered basal chow as well as a cholesterol (0.8%) control diet over an eight months feeding period to rabbits of both 10 g/kg DC 360 (350 cSt.) and 10 g/kg DC Antifoam A with and without the 0.8% cholesterol supplement, Carson and coworkers (1966) concluded that cholesterol, rather than the siloxanes, was the prime cause of tissue damage.

In a very brief summary, Hobbs (1973) indicated that Mallard Ducklings and Bobwhite Quail showed an LC_{50} of over 5 g dimethylpolysiloxane/kg feed in 8 days _ad libitum_ feeding. Hobbs (1973) also indicates that current research is underway to assess the toxicity of dimethylpolysiloxane on young chickens.

ii) Injections: I.V., I.M., Subcutaneous, Intraperitoneal, Intra-articular:

The only reason that these various types of injections are considered in the same section is that they are non-controversial and present little difficulty in interpretation.

DC Antifoam A administrered to dogs I.V. into the right jugular vein had a LD_{50} of 0.9 - 1.0 ml/kg body weight. Death was characteristic of massive obstruction of the pulmonary artery or branches. In fatal cases, the right ventricle evidenced extreme distension not noted in surviving animals. Arterial administration via the carotid artery gave a much smaller LD_{50} of 0.02 ml/kg body weight. Here, fatal cases showed necrosis due to impeded blood flow to the brain, and some survivors showed neurologic damage with limited brain damage as above (Reed and Kittle, 1959).

Intramuscular (I.M.) administration of 1.0 cc of a dimethylsiloxane (Dri-Film #9977) resulted in slight macrophage infiltration and limited muscle fiber necrosis in rabbits, whereas identical subcutaneous dosages showed no response (Kern et al., 1949). These results agree well with those showing that only hexamethyldisiloxane causes appreciable irritation subcutaneously in rabbits. Intraperitoneal and intradermal applications of the polysiloxanes indicate negligible toxic effects (Rowe et al., 1948). Dimethylpolysiloxane fluid injected into the synovium of the rabbit knee produced mild inflammatory response (Donahue et al., 1971).

iii) Intravetreous Injection:

The use of DC 360 Medical Fluid (2000 cSt.) is of particular interest because current investigators differ widely on their opinion of its histopathic potential. Lee, Mukai, and coworkers contend that large numbers of silicone particles appear in the retina 2 - 3 hours after injection and cause degenerative lesions. They base these findings on electron microscopic and histochemical surveys (Mukai et al., 1972; Lee et al., 1969). Labelle and Okum (1972) label the above microscopic findings as artifacts and report negative toxicity in their experimental work. Resolution of these conflicting results should prove critical to an understanding of both silicone transport in a membrane system and possible biochemical mechanisms for silicone toxicity.

iv) Toxicity from Inhalation and Dermal Absorption:

Silicones have shown little appreciable toxicity via these routes. The higher siloxanes have extremely low volatility and do not cause toxic effects on inhalation. Similarly, because they are not easily absorbed through the skin, the cutaneous toxicity seems negligable (Hecht, 1968).

However, hexamethyldisiloxane is relatively volatile and in a saturated atmosphere (40,000 ppm) will lead to mortality in guinea pigs after exposure periods of 15 to 20 minutes. At lower concentrations or on shorter periods of exposure, the toxic effects are greatly reduced or disappear (Rowe et al., 1948). Thus, this type of toxic response seems to have little environmental importance.

2. Chronic Toxicity

Chronic toxicity studies have been conducted in long term feeding of rats and dogs with DC Antifoam A. In both cases, no toxic signs are manifest. Rats, over a two year feeding period of 3g/kg feed (DC Antifoam A) show no pathological signs that can be clearly associated with silicone adminstration (Rowe _et al._, 1950). Similarly, dogs show no toxic effects with oral administration of up to 3g/kg feed over a six month period (Child _et al._, 1951). In that the normal usage range of DC Antifoam A is from 10-25 mg/kg, little toxic potential seems indicated.

3. Sensitization

In the only study available, no antigen/antibody-type sensitization could be stimulated in the guinea pig by administration of dimethylpolysiloxane. Needless to say, this is hardly sufficient evidence for ruling out the possibility of such a response from other organisms (Nosanchuk, 1968). However, it seems probable that if there was an appreciable potential for human sensitization, it would have already appeared as a problem in industrial hygiene. Thus far, no such responses are reported (Hobbs, 1973).

4. Teratogenicity

Only one case of silicone induced teratogenicity is available in the literature surveyed. An equilibrated copolymer of phenylmethylcyclosiloxanes and dimethylcyclosiloxanes (PMxMMy) administered at 220mg/kg/day to pregnant rats from the 16th day of pregnancy caused urogenital malformation in the female - but not male - pups, accompanied by an inability to control urine flow (LeFevre _et al._, 1972). In an earlier study, a much more widely used variety of silicone, DC 200 (viscosity not specified) was found not to produce teratogenic effects in rats with oral doses of up to 3.8g/kg/day when administered from the sixth to the fifteenth day of pregnancy (Barry, 1973).

5. Carcinogenicity

Hueper (1964) using a polydimethysiloxane sheet (200mg, 11 x 8 x 2 mm) implanted subcutaneously in 35 rats induced 10 cancerous tumor formations. These all involved smooth walled cavity tumors which contained the silicone sheet loosely inside. Similar results were obtained by Maeda (1971). Although these results indicate caution in the use of silicone prosthetic implants in man, the possible environmental correlations seem limited.

6. Mutagenicity

No detailed study on silicone mutagenicity was encountered. Hobbs (1973) reports of a study indicating that a dimethylpolysiloxane fluid is not mutagenic in albino mice. Drosophila has recently been the subject of a pilot study of the mutagenic activity of some organosilicones (Bennett, 1973), but the results have not been screened for this report.

7. Behavioral Effects - Reproductive Activity

A recent series of papers has indicated that certain cyclic siloxanes show a pronounced effect on the sexual physiology of various non-human mammals. The equilibrated copolymer phenylmethylcyclosiloxanes and dimethylcyclosiloxanes (PMxMMy) had been in common use in the cosmetic industry (Olson, 1972). In rabbits, however, this polymeric mixture was found to produce marked testicular atrophy and spermatogenic depression both in dermal and oral administration. Similar effects were noted in oral but not dermal applications to monkeys (Palazzolo _et_ _al_., 1972). LeFevre and coworkers (1972) noted the previously discussed teratogenic effects of this mixture as well as indicating a general interruption of the estrous cycle in female rats. PMxMMy constituents and related cyclosiloxanes were shown to inhibit reproductive ability in male mice, rats, and rabbits (Bennett _et_ _al_., 1972). This antiandrogenic activity is paralleled by the estrogenic activity of these same compounds in the females of the species (Hayden and Barlow, 1972). The relative activities of the compounds studied are summarized in Table X [from Hayden & Barlow, 1972].

Table X

Comparative Relative Activities of 32 Organosiloxane Compounds
Based on Effects on the Ovariectomized Immature Female Rat Uterus
Following Oral Administration
[Hayden and Barlow, 1972];
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Compound	Relative activity[a]
A. *Substituted siloxanes*	
Disiloxanes	
Phenyl substituted	
$PhMe_2SiOSiMe_3$	0
$PhMe_2SiOSiMe_2H$	0
$PhMe_2SiOSiMe_2Ph$	+2
$PhVinylMeSiOSiMe_3$	+1
$Ph_2MeSiOSiMe_3$	0
$(PhCH(CH_3)CH_2)Me_2SiOSiMe_3$	+1
Trisiloxanes	
Phenyl substituted	
Linear	
$Me_3SiOSiPhOHOSiMe_3$	0
$Me_3SiOSiPhHOSiMe_3$	+1
$Me_3SiOSiPh_2OSiMe_3$	+1
Cyclic	
$[(PhMeSiO)(Me_2SiO)_2]$	+2
$[(PhMeSiO)_2(Me_2SiO)]$	+3
2,4-*trans*-$[(PhMeSiO)_2(Me_2SiO)]$	+3
2,4-*cis*-$[(PhMeSiO)_2(Me_2SiO)]$	0
cis-$[(PhMeSiO)_3]$	+1
trans-$[(PhMeSiO)_3]$	+1
Tetrasiloxanes	
Cyclic	
$[(PhMeSiO)(Me_2SiO)_3]$	+4
$[(o\text{-}tolylMeSiO)(Me_2SiO)_3]$	+3
$[(HMeSiO)(Me_2SiO)_3]$	0 – +1
$[(VinylMeSiO)(Me_2SiO)_3]$	0 – +1
$[(n\text{-}PrMeSiO)(Me_2SiO)_3]$	0 – +1
$[(PhMeSiO)_4]$	+1
$[(Me_2SiO)_4]$	+1
$[(PhMeSiO)_2(Me_2SiO)_2]$ (racemic mixture)	+4
2,4-*cis*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+1
2,6-*trans*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+3
2,6-*cis*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+4
$[(PhHSiO)(Me_2SiO)_3]$	+3
$[(Ph_2SiO)(Me_2SiO)_3]$	+1
$[(PhOHSiO)(Me_2SiO)_3]$	+1
B. *Miscellaneous*	
$OHMe_2SiPhSiMe_2OH$	0
$PhMe[SiCH_2CH_2SiMePhO]$	+3
$[(Me_2SiNH)(Me_2SiO)_3]$	+1
$(Me_3SiO)_3SiPh$	0

[a] Code: 0 = No effect; +1 = statistically nonsignificant increase $<20\%$; +2 = statistically significant increase at 0.05 level of significance; +3 = statistically significant increase at 0.01 level of significance; +4 = increase equal to or greater than estrogen treated controls.

While presenting a useful tool for research into hormonal behavior (LeVier and Jankowiak, 1972), the environmental significance of these findings is uncertain. The hormonally active compounds are no longer available commercially. Other polysiloxane fluids that are more widely used do not demonstrate any similar activity (Hobbs *et al.*, 1972).

C. Toxicity to Lower Animals

Toxicity studies encountered on non-mammals have concentrated primarily on various antifoams in an aquatic environment.

Fish seem quite tolerant to relatively high concentrations of silicone. SAG-10, a dimethylsilicone oil and silica emulsion, and SAG-530, a dimethylsilicone-oxyalkylene, both of Union Carbide, have no toxic effects on the fathead minnow in concentrations up to 2,000 mg/l over a four day exposure period (Spacie, 1972). Similarly, 1% DC Antifoam C(0.3% DC200), another dimethylsilicone, has no toxic effects on rainbow trout or bluebill sunfish over the same period of exposure as above (Barry, 1973).

Daphnia, however, show a much more pronounced toxic response [See Table XI from Spacie, 1972].

Table XI

[Spacie, 1972]

Daphnia Mortality (%) in SAG 10 Solutions

	Concentration - mg/l						
Hours	0	1	10	100	500	1,000	2,000
24	0	0	20	10	40	30	60
48	0	20	20	10	40	50	100
96	0	30	40	40	50	100	100

Daphnia Mortality (%) in SAG 530 Solutions

	Concentration - mg/l						
Hours	0	1	10	100	500	1,000	2,000
24	0	0	0	0	10	10	40
48	0	0	0	0	10	30	60
96	10	0	10	10	20	80	100

The 96 hour LC_{50} of 500 mg/l SAG-10 and 500-1,000 mg/l SAG-530 might seem to indicate that these compounds are relatively non-toxic. However, LC_{50}'s are not absolute indicators of toxicity. Note that after 96 hours a 30% Daphnia mortality is achieved at 1 mg/l SAG-10, approximately 1 ppm. Needless to say, a 30% mortality of this important food source in aquatic systems would create considerable environmental stress. Thus, while this experiment was meant only as a preliminary evaluation and not as a definitive study, Spacie's conclusion that further studies are not required because of the high LC_{50}s is questionable. Detailed investigations on Daphnia and other environmentally critical invertebrates in aquabiotic systems seem mandatory. Dow Corning has a preliminary study on Daphnia underway (Hobbs, 1973).

No further toxicity studies were found. Unspecified silicones at 0.1 - 2.0% diet are reportedly fed to silkworms to increase body and cocoon weights, but no adverse effects are given (Hashimoto *et al.*, 1972).

D. Plant Toxicity

Parkinson (1970) has applied dimethylpolysiloxanes (1,000 and 12,500 cSt.) to leaf surfaces of short grass, certain farm crops and trees as antitranspirants. While these applications have proven effective in conserving water, no toxic effects have been noted. A more detailed investigation of the antitranspirant effect of these silicones is in progress. No toxic effects have been noted thus far on 32 plant species (Bennett, 1973).

E. Microorganism Toxicity

Various fluid polydimethylsiloxanes have been found to elicit no toxic response from the following bacteria: *E. coli*, *P. aeruginosa*, *A. aerogenes*, *S. aureus*, *B. megaterium*, and *B. subtilis* (Bennett, 1973). Similarly, unspecified polydimethylsiloxanes and polyphenylmethylsiloxanes have shown no fungicidal properties (Sharp and Eggins, 1970). Along with the negative microbiocidal properties of liquid silicones, silicone rubber surfaces seem to offer a satisfactory growth surface for certain fungi (Calderon and Staffeldt, 1965; Ross, 1963).

XI. Silicones: Summary and Conclusions

Because of their unusual physical and chemical properties, siloxanes enjoy a widening range of utility and a progressive development of established uses. In that production figures often include various non-siloxane additives, a precise determination of production growth is not possible. Yet, based on the available data, siloxane production has probably doubled and may have tripled since 1965. A projected annual growth rate of 10% is probably not excessive. Of the three basic types of siloxanes, the fluids (primarily dimethyl - and phenylmethylsiloxanes), which comprise over half of the total market, are likely to achieve the greatest environmental exposure. Their uses in waxes, polishes, cosmetics, antifoaming agents, food additives, textile finishings, and water repellant surfaces indicate probable environmental exposure. Although they are relatively hydrophobic, they can form aqueous emulsions with little difficulty and the possibilities of water transport and eventual distribution in aqueous systems seems reasonable. Also, the vapor pressures of the fluid siloxanes are low but not negligible and may allow for significant atmospheric transport. Unlike the fluids, siloxane rubbers would seem less available for environmental exposure because they are used in comparatively nondisposable products (e.g., insulators, plastic parts) and are less easily transported because of their bulk and/or surface binding properties. Similarly, siloxane resins are tightly bound in polymeric formulations. Also, because of their very limited use and high cost they are not likely to be released into the environment in large amounts. Thus, considering the physiochemical properties, production values, and current uses, the fluid siloxanes seem to represent the greatest source of environmental contamination. The proposed use of dimethylpolysiloxane fluids as plant antitranspirants will result in significant terrestrial exposure. To what extent these fluids will leach into aquatic systems is yet to be determined.

Once released into the environment, siloxanes would seem to be extremely stable under normal physical and chemical conditions. Rates of environmental hydrolysis, photolysis, oxidation, etc. are probably low and may be negligible. Thus, with continued production and concomitant release, siloxanes may accumulate in the environment unless biologically deteriorated. Such activity does not seem likely. Phylogenetically advanced life forms are not noted for their adaptability and the metabolic degradation of siloxanes would seem to require some radical enzymatic innovation. Acid cleavage in some mammalian stomachs (e.g., dog, pH 1.0-4.5; rabbit, pH 1-1.6; sheep, pH 1.02-1.32) while a possible route of deterioration has not been reported and even if proven would probably be of too little volume to be of gross environmental importance. Microorganisms may have the potential to degrade siloxanes, but such degradation has not yet been conclusively demonstrated. In fact, most tests so far indicate that siloxanes should be quite persistant.

Given that significant amounts of at least liquid siloxanes may be released, and may possibly persist and accumulate in the environment, a reasonable determination of the potential hazard that they pose must be based on quantitative knowledge of not only the degree of contamination, but also the levels that might be detrimental or lethal to representative groups of life forms. Neither of these factors have been satisfactorily described.

Monitoring data on environmental levels of siloxanes were not found in the literature. Such information should soon become available and must be critically screened in any assessment of potential siloxane hazard. Further, since the level of siloxanes may steadily increase with time, such monitoring reports should be made periodically.

Even once the environmental concentrations are known, establishing their significance will be difficult in view of the current understanding of siloxane toxicity. Clearly, much of the acute lethality data has only tangential relevance. Massive doses of any foreign substance are liable to produce adverse responses that may be entirely unrelated to low level exposure pathology. Studies on chronic mammalian toxicity do seem to indicate that commercial siloxanes are not likely to pose any threat to mammalian health. Similarly, bacterial and fungi do not seem to exhibit a toxic response to siloxanes.

This lack of toxicity is probably best explained in terms of biological non-availability. In mammalian feeding, long chain siloxanes do not seem to be transported across the gastrointestinal tract and thus the internal organs are not exposed. Rabbits, and other mammals with a low gastric pH, may be an exception. Whether or not highly acidic gastric secretions can cause polymeric cleavage and subsequent absorption should be determined. Negative toxicity in unicellular organisms may also be explained on the basis of low membrane permeability of long chain siloxanes. It seems reasonable to assume that siloxanes seldom cross the cell membrane. Even if phagocytized coincident with food particles, the siloxanes would still be bound by a vacuolar membrane and possibly eliminated unchanged without protoplasmic contact.

Even accepting the low order of mammalian and microbiol toxicity, a rather large gap in the present state of siloxane toxicology is evident and comprised of the lack of toxicity data on the non-mammalian vertebrates and the invertebrates.

Dow Corning is presently conducting research on the possible toxic effects of some dimethylpolysiloxanes to birds. In that these siloxanes may be found in the terrestrial environment, these studies are vital and deserve careful attention. Data thus far available on fish consist of four-day exposure experiments. These can offer no more definitive environmental information then do acute toxicity studies in mammals. Other important vertebrates such as the amphibians and reptiles have not been studied.

The invertebrates, especially the insects and lower aquatic phyla, are critical links in the food chain. While many possess the type of membrane systems that would seem to protect them from siloxane exposure, this assumption should at least be tested. Information available on the invertebrates is limited almost entirely to Daphnia. Here, the high incidence of mortality at 1 ppm is hardly conclusive but nonetheless somewhat disconcerting in that a primary sight of siloxane environmental contamination may be the aquatic environment. Daphnia, like many of the aquatic invertebrates, are filter feeders. This involves particle clearance by passing relatively large volumes of water over collecting surfaces. That siloxane molecules may adhere to food particles and/or be ingested along with such particles cannot be ruled out. Once ingested, the possibility that these molecules might accumulate in fatty tissue, excretory organs, or other areas should be considered. Another possibility, especially in the smaller invertebrates, that the feeding apparatus might be fouled should also be examined. Similar speculations on possible modes of siloxane pathology in terrestrial invertebrates could also be devised. The point is that experimental evidence on critically important invertebrate groups is not available.

In summary, if there is any danger from the environmental contamination of siloxanes it will most probably come from the liquid siloxanes and be located in aquatic systems. The damage might be tissue response to accumulation of long chain siloxanes and/or cellular absorption of lower molecular weight siloxanes after chain cleavage. However, siloxanes are eminently useful compounds and current information indicates that they may have a low order of biological activity. Nevertheless, the possible dangers outlined above deserve evaluation.

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FLUOROCARBONS

I. Physical Properties

The fluorohydrocarbon compounds, in comparison to hydrocarbons, have a number of interesting physical properties. The fluorocarbons have a higher liquid density; for compounds with four or less carbons, the boiling points of the fluorinated compounds are slightly higher; with more than four carbons, the boiling points are generally lower than the corresponding hydrocarbons. The fluorocarbon viscosities are similar to the hydrocarbons but change more with temperature. The fluorocarbon surface tension is low and dielectric properties are good.

The chlorofluorocarbons have similar properties to the fluorohydrocarbons. They usually have high density, low boiling point, low viscosity and low surface tension. In addition, many of these compounds have vapor pressures falling somewhere between 15 and 100 psig, as computed at 70°F, which allows their use in the aerosol industry. The physical properties of the bromo- and iodofluorocarbons are similar to those of the chlorofluorocarbons, except for higher densities. Some physical properties of most of the commercially important fluorocarbons are shown in Table I. Table II presents the physical properties of polytetrafluoroethylene.

TABLE I

Physical Properties of Commercially Important Fluorocarbons
(Sage, 1963; Downing, 1966;)

Compound	Cl_3CF	Cl_2CF_2	$ClCHF_2$	$Cl_3C_2F_3$	$Cl_2C_2F_4$	ClC_2F_5	$ClC_2H_3F_2$	$C_2H_4F_2$	C_2F_4	$BrCF_3$	C_4F_4	$-(CF_2-CF_2)-_x$
Fluorocarbon Number*	11	12	22	113	114	115	142b	152a	1114		(cyclic) C318	
boiling point, (°C)	23.8	-29.8	-40.8	45.7	3.1	-38.7	15.1°F	-24.7	-76.3	-57.8	-5.9	
freezing point (°C)	-111	-158	-160	14	-60	-106	-204 °F	-117	-142.5	-168	-41	327
vapor pressure (psia) (70°F)	13.4	70.2	122.5		12.9		29.1	61.7			25.4	
solubility in water (wt %)	0.11	0.028	0.30	0.017	0.013	0.006	0.054	0.17		0.03	0.014	
liquid density g/ml	1.476/25°C	1.311/25°C	1.194/25°C	1.579/20°C	1.468/70°F	1.291/25°C	1.119/70°F	0.966/19°C	1.519/-76°C	1.538/25°C	0.620/25°C	
crit. temperature (°C)	198.0	112.0	96.0		145.6	80.0			33.3	67.0	115.3	
crit. pressure (atm)	43.2	40.6	49.1		32.5	30.8			572 psig	39.1	27.5	
surface tension (dynes/cm at 77°F)	19	9	9									

* Units digit= # of F atoms; tens digits = # of H atoms +1; hundreds digit = # of C atoms -1; thousands digit = # of double bonds.

TABLE II

Typical Physical Properties of Polytetrafluoroethylene (Sherratt, 1966); reprinted by permission. Copyright 1966, J. Wiley and Sons

Property	Value	Method
tensile strength at 23°C, psia	2500-4000	D638-58T
elongation at 23°C, %	200-400	D638-58T
flexural strength at 23°C	did not break	D790-59T
stiffness at 23°C, psia	60,000	D747-58T
impact strength, izod, (ft)(lb)/in.		
−57°C	2.0	D256-56
23°C	3.5	D256-56
77°C	6.0	D256-56
hardness, durometer, D	55-70	D1706-59T
compressive stress at 1% deformation at 23°C, psia	600	D695-54
deformation under load at 50°C, %		
1200 psia, 24 hr	4-8	D621-59
2000 psia, 24 hr	25	D621-59
deflection temperature under a load of 66 psi, °C	121	D648-56
coefficient of linear thermal expansion per °C, 25-60°C	9.9×10^{-5}	D696-44
thermal conductivity,[b] 0.18 in., cal/(sec)(cm²)(°C)(cm)	5.8×10^{-4}	D696-44
specific heat, cal/(g)(°C)	0.25	
water absorption, %	0.0	D570-59T
flammability	nonburning	D635-56T
specific gravity	2.1-2.3	D792-50
resistance to weathering	excellent[c]	

[a] Tests have been performed by ASTM methods unless otherwise indicated. Data shown are average values and should not be used for specifications.

[b] Thermal conductivity measured by Cenco-Fitch apparatus.

[c] No detectable change after ten years of outdoor exposure in Florida.

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II. Production

Fluorocarbon compounds are produced in the United States by six major chemical manufacturers. Table III lists the U.S. companies, the products they produce, their plant capacity, and geographical location. In some other countries, fluorocarbon products and manufacturers are: In England, Arcton (ICI), Isceon (Imperial Smelting); in West Germany, Heydogen (Chemische Fabrik von Heyden), Frigen (Farbwerke Hoechst), Kaltron (Kali-Chemie); in France, Flugene (Pechiney), Forane (Ugine); in Italy, Algofrene (Montecatini), Edifren, (Sicedison); in the Netherlands, Fresane (Uniechemie); in East Germany, Frigedohn; in Russia, Eskimon; in Argentina, Algeon (Fluoder), Frateon (I.R.A.); in Japan, Daiflo (Daikin Kozyo), Asahiflon (Asaki Glass). The capacity for these foreign manufacturers was estimated at 900 million lbs. in 1972 (Noble, 1972).

The fluorocarbon industry has been growing at a fast pace. During the period 1962-1972 the annual growth rate was 8.5% and a growth rate of 6.5%/year through 1977 is projected (Chemical Marketing Reporter, 1973). Table IV reviews the growth in the industry by major compounds that have reported production (or sales) levels.

TABLE III

Fluorocarbon Producers and Capacities
(Lutz, et al. 1967, Chemical Marketing Reporter, 1973)

Company	Trade Names	Plant Capacity 10^6 lb./yr. in 1973	Plant Locations
Allied Chemical Corporation	Genetron Genesolve Halon TFE Plaskon CTFE	310	Baton Rouge, La. Elizabeth, N.J. Danville, Ill. El Segundo, Calif.
E. I. du Pont de Nemours and Company	Freon Teflon TFE Vitron	500	Antioch, Calif. Carney's Point, N.J. East Chicago, Ind. Louisville, Ky. Montague, Mich.
Kaiser Aluminum and Chemical Corporation	Kaiser	50	Gramercy, La.
Minnesota Mining and Manufacturing Company	Kel-F-81 and 82 Fluorel	5 (1967)	Decatur, Ala.
National Rolling Mills Company	--	25 (1967)	Malvern, Pa.
Pennwalt Chemical Corporation	Istron Kynar	115	Calvert City, Ky. Thorofare, N.J.
Racon	--	20	Wichita, Kan.
Thiokol Chemical Corporation	Thiokol TFE	2	Moss Point, Miss.
Union Carbide Corporation	UCON	150	Institute, W.Va.

TABLE IV

Production and Capacities of Fluorocarbons
(Chemical Marketing Reporter, 1973; U.S. Tariff Commission,
1961-1971; Stanford Research Institute, 1973)

Compound	Fluorocarbon Capacity		Chlorodifluoromethane		Dichlorodifluoromethane		Trichlorofluoromethane		Dichlorotetrafluoroethane		Resins and Elastomers	
Fluorocarbon #			22		12		11		114			
	(10^9g)	(10^6 lbs.)	(10^9g)	(10^6 lbs.)	(10^9g)	(10^6 lbs.)	(10^9g)	(10^6 lbs.)	(10^9g)	(10^6 lbs.)	(10^9g)	(10^6 lbs.)
1961	235.9	520	10.9	24*	78.5	173	41.3	91	4.1	9		
1962	254.0	560	13.2	29*	94.3	208	56.7	125	5.0	11		
1963	276.7	610	16.3	36*	98.4	217	63.5	140	5.4	12		
1964	299.4	660	19.5	43*	103.4	228	67.1	148	5.9	13		
1965	326.6	720	22.7	50*	122.9	271	77.1	170	10.0	22	5.4	12
1966	326.6	720	25.4	56*	129.7	286	77.1	170	7.7	17*		
1967	326.6	720	26.8	59*	140.6	310	82.6	182	10.0	22*		
1968	326.6	720	24.9	55*	147.9	326	92.5	204	7.7	17*		
1969	435.5	960	32.2	71*	166.9	368	107.9	238			7.7	17
1970	444.5	980	33.1	73*	170.1	375	110.7	244			7.3	16
1971p	458.1	1010	36.3	80*	176.9	390	117.0	258				
1972												
1973	519.4	1145										

*Sales

III. Uses

The uses of fluorocarbons are dependent somewhat upon their physical-chemical properties and physiological activity. Table V lists the major uses and size of the market as well as the fluorocarbons compounds utilized.

The major fluorocarbon use is for aerosol* propellants. Although this use is the backbone of the industry, its percentage of the market has decreased in the last few years (1964 - 60%, 1973 - 50%) (Noble, 1972). The major industrial products used in this category are dichlorodifluoromethane (12), trichlorofluoromethane (11), dichlorotetrafluoroethane (114), and small amounts of octafluorocyclobutane (C318). Fluorocarbons find use in this application because they meet the following criteria: (1) appropriate vapor pressure; (2) relatively nontoxic; (3) chemically inert so they do not react with the active ingredients; and (4) nonflammable and nonexplosive (Sage, 1963).

The second largest use for fluorocarbons is as a refrigerant for air conditioning and refrigeration systems. The principal compounds used are dichlorodifluoromethane (12) and chlorodifluoromethane (22). This was the very first application of fluorocarbons and they quickly replaced older refrigeratns because of their inertness and low toxicity. A significant growth in this area occurred in the early 1960's with an increase in the use of auto, home, and commercial air conditioning.

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*"Self-dispensing, pressured, self-propelling products, dispensed by the use of a liquefied, nonliquefied, or noncondensed gas." (Sage, 1963)

TABLE V

Uses of Fluorocarbons
(Chemical Marketing Reporter, 1973)

Use	Percentage of the Market	Fluorocarbons*
Aerosol propellants	50%	12, 11, 114
Refrigerants	28%	12, 22
Plastics	10%	1114, 1216, 1132, 1113
Solvents	5%	113, 11, 214
Blowing agents, exports, and miscellaneous	7%	

*Units digits = # of F atoms; tens digits = # of H atoms +1; hundreds digits = # of C atoms -1; thousands digit = # of double bonds.

Fluorocarbon polymers, or fluoroplastics, provide a sizable category of fluorocarbon use. Polytetrafluoroethylene (PTFE) (1114) is one of the major fluoroplastics. Its major applications are in the following categories: wire and cable insulation; gaskets, seals, valves, diaphragms, chemical hose, etc.; laboratory ware; threaded pipe joint sealant; packings, bearings, and piston rings; and non-stick surface coatings. Other fluorocarbon plastic products include copolymers of tetrafluoroethylene (1114) and hexafluoropropylene (1216), copolymers of vinylidene fluoride (1132) and hexafluoropropylene (1216) and polymers from chlorotrifluoroethylene (1113) and from vinylidene fluoride (1132).

Fluorocarbon use in the solvent and degreasing field has grown in recent years as measured by market percentage (1963 = 2.3%, 1973 = 5.0%) (Downing, 1963; Chemical Marketing Reporter, 1973). The solvent most widely used is trichlorotrifluoroethane (113) with small amounts of trichlorofluoromethane (11) and tetrachlorodifluoroethane (112) being used. These solvents find special use for dissolving oils and greases without affecting plastic, elastomeric or metal components. Lutz _et_ _al_. (1967) have suggested that trichlorotrifluoroethane (113) may challenge perchloroethylene in the dry-cleaning-solvent field.

Fluorocarbons are also used as blowing agents to impart, for instance, the thermal insulation properties of urethane foams. Other uses include applications as general anesthetics (Halothane, $CHBrClCF_3$); dielectric fluids; fire-extinguishing agents ($CBrF_3$, $CBrF_2CBrF_2$); and as pressurized leak-testing gases in wind tunnels and in bubble chambers. New applications which may provide a sizable market are uses as a solvent in Rankine cycle engines, in immersion freezing of foods (Bucholz and Pigott, 1972), and as a drycleaning solvent (Noble, 1972).

IV. Current Practice

Fluorocarbons, which are gases at ambient temperatures, are shipped in tank cars, tank trucks and steel cylinders ranging from approximately 10 lbs. to several tons. Fluorocarbon solvents (e.g., 11, 112 and 113) are transported in tank cars, tank trucks, or in steel drums. Drum sizes range from 5 to 55 gallons.

The fluorocarbons for the most part are nonflammable and, thus, do not present a fire hazard. The pure compounds are stable, nonirritating, and have a low order of toxicity. However, combustion products (halogens, halogen acids, and carbonyl halides) from contact with a flame or hot metal surfaces are corrosive, irritating and toxic when inhaled.

The high cost of fluorocarbons ($.25/lb. and up) suggests that very little is disposed of on purpose. Correspondence with major manufacturers indicates that large quantities of material contaminated or no longer needed are often reclaimed by the manufacturer at their processing facilities.

V. Environmental Contamination

Because of the high volatility and chemical stability of fluorocarbons, these chemicals are likely to be released to and persist in the environment. Their immediate fate from their use as aerosol propellants is atmospheric release. Partial losses are also expected from their use as solvents and refrigerants. Korte and Klein (1971) and Iliff (1972) have briefly discussed environmental pollution potential from fluorocarbons.

Very low concentrations of trichlorofluoromethane and dichlorodifluoromethane have been detected in both water and air environmental samples. Lovelock (1971) detected trichlorofluoromethane at concentrations of 10 to 190 x 10^{-12} by volume in the air over southwest Ireland. Highest concentrations were found when easterly winds from continental Europe were observed, thus indicating the source of the fluorocarbons as being from the industrially developed European continent. Su and Goldberg (1973) were able to detect both trichlorofluoromethane and dichlorodifluoromethane. Samples were taken in LaJolla, San Diego, and in the desert region 100 km northeast of San Diego, California. In the desert, which is perhaps more representative of a background level, a concentration of 0.097 and 0.70 x 10^{-9} ml per ml air was detected for trichlorofluoromethane and dichlorodifluoromethane, respectively. The authors attributed the higher concentration of dichlorodifluoromethane to slightly higher production levels and greater environmental stability.

VI. Monitoring and Analysis

Development of analytical techniques for determining fluorocarbons in trace amounts was first undertaken in order to allow the use of fluorocarbons as a tracer of atmospheric dispersion. Schultz (1957) found that dichlorodifluoromethane was a promising tracer chemical. He used a modified ionization-type leak detector which was sensitive to a concentration of approximately 1 ppm; however he was plagued by non-reproducibility (Collins et al., 1965).

Marcali and Linch (1966) reported a colorimetric method for perfluoroisobutylene and hexafluoropropene in air samples capable of detections at 0.1 ppm and 0.02 ppm, respectively. The method is based on a chemical reaction between the fluorocarbon and pyridine and piperidine in methanol (collection solvent) due to the unsaturated system (X-C = CF_2, X = halogen) and, therefore, is only good for unsaturated fluorocarbons.

McFee and Bechtold (1971) studied a combined pyrolyzer-microcoulomb detector system as a continuous monitoring system. The limits of detection for trichlorotrifluoroethane and tetrachlorodifluoroethane were 0.3 ppm and 0.9 ppm, respectively. The authors suggested that this instrument would be useful for testing air cleaning systems and for measuring toxicants with low threshold limit values.

Shargel and Koss (1972) used a gas chromatographic method with electron-capture detection for determining chlorofluorocarbons in dog blood. The method used a hexane extraction and the lower limits of quantification were 3.3, 10, 40, and 80 μg/l of blood for trichlorofluoromethane, dichlorodifluoromethane, trichlorotrifluoroethane, and dichlorotetrafluoroethane, respectively.

Collins and Utley (1972) studied the possible use of mass spectrometry for detection and identification of organic pollutants in the atmosphere. They used a silicone rubber membrane direct inlet system (similar to GC-MS interfaces) which allowed 1000 fold increases in minor components of air. With this system, they could detect trichlorotrifluoroethane at 0.1 ppm.

Two techniques have been used to detect fluorocarbons in air at the ppt (10^{-12}) concentration ranges; (1) direct analysis of air-fluorocarbon mixtures with gas chromatography with an electron-capture detector (GC-EC), and (2) sampling tube concentration with gas chromatography and flame ionization detection (GC-FI). Collins et al. (1965) used the GC-EC technique to study the use of sulphur hexafluoride and dichlorodifluoromethane as gas air tracers. They found the sensitivity for dichlorodifluoromethane to be only in the 50 to 100 ppb range. Saltzman et al. (1966) used a similar GC-EC system with bromotrifluoromethane and octafluorocyclobutane. A sensitivity of about 0.3 ppb was achieved without concentrating the sample.

Gelbicova-Ruzickova et al. (1972) developed a method for determining minute quantities of halothane (2-chloro-2-bromo-1,1,1-trifluoroethane) in the air of operating theatres. They used a porous polymer packing (Porapak P and Q) in a sampling tube to preconcentrate the sample. Detection was carried out with a flame ionization detector (GC-FI). Concentrations down to 10 ppb could be determined. These authors noted a low stability of the electron capture detector (and, thus, the use of flame ionization) if the electrodes are contaminated by large amounts of water vapor and oxygen. However, Lovelock and coworkers (Lovelock, 1971, 1972; Lovelock et al., 1973) and Su and Goldberg (1973) have found gas chromatography with an electron capture detector to be quite satisfactory for determining trichlorofluoromethane and dichlorodifluoromethane at approximately 1 ppt and 45 ppt by volume, respectively. Lovelock used experimental conditions where the ionization in the detector is complete, making the system coulometric. He (Lovelock, 1971) notes that other halocarbons such as difluorodichloromethane and perfluorocyclobutane were not detected because of their low sensitivity in the electron-capture detector.

Clemons and Altshuller (1966) reviewed the electron-capture detector sensitivity of a number of halogenated substances. Table VI lists those results and compares them to flame-ionization detection. The figures show that for many compounds (ones with less than 2 chlorines) flame-ionization detection is just as sensitive as electron-capture. However, because the electron-capture detector is specific for halogenated substances, it is often used even when the flame-ionization detector would be more sensitive.

VII. Chemical Reactivity

Fluorocarbons have unusually high thermal and chemical stability. The fluorinated hydrocarbons are the most stable. They will react with molten alkali metals but are not affected by acids or oxidizing agents. The stability is dependent upon the number of carbons and the hydrogen/fluorine ratio; the lower the number of carbons and H/F ratio, the higher the thermal stability. For example, carbon tetrafluoride shows no reaction with copper, nickel, tungsten, or molybdenum at 900°C, whereas compounds of higher molecular weight decompose at temperatures about 400°C. Compounds with only one fluorine atom are quite reactive (Downing, 1966).

Substitution with other halogen atoms decreases the chemical stability. The chlorofluorocarbons are the most stable halofluorocarbons. They do not react with most metals below 200°C or with acids or with oxidizing agents

TABLE VI

Electron-Capture Detector Response to Various Fluorinated Compounds
(Clemons and Altshuller, 1966)

Compound	Fluorocarbon #	Response (sq.in. ppm)	Response Flame-ionization (sq.in. ppm) (all compounds)
SF_6		580	0.1-1.0
$CFCl_3$	11	370	
$(CF_3)_2C{=}CF_2$	1218	90	
$ClF_2C{-}CFCl_2$	113	50	
$\underline{CF_2CF_2CF_2CF_2}$	C318	30-40	
CF_3Br	13B1	12-40	
CF_2Cl_2	12	9	
ClF_2CCF_2Cl	114	2	
$CF_2{=}CCl_2$	1112	0.2	
$CHFCl_2$	21	5×10^{-2}	
CF_3CF_2Cl	115	5×10^{-2}	
$CF_2{=}CFCl$	1113	3×10^{-2}	
CF_3Cl	13	1×10^{-3}	
CHF_2Cl	22	3×10^{-3}	
CF_4	14	3×10^{-4}	

and react only very slowly with alkali in the presence of water. However, they are decomposed by molten alkali metals (e.g., dichlorodifluoromethane reacts vigorously with aluminum). Reaction rates of hydrolysis in neutral aqueous solutions at room temperature are quite slow (Stepakoff and Modica, 1973). Sanders (1960) has reported a free-radical type of reaction between trichlorofluoromethane and alcohols (biological significance unknown). The chlorofluorocarbons are not quite as thermally stable as the fluorocarbons but still show high stability relative to most organic compounds. Again, the thermal stability is proportional to the fluorine content in the molecule (Trenwith and Watson, 1957; Calleghan, 1971). With bromo- and iodofluorocarbons, the stability of the compound decreases as the ratio of bromine or iodine to fluorine increases (Downing, 1966).

The monomers of the fluorocarbon plastics [e.g., tetrafluoroethylene (TFE)] are much less stable than the saturated fluorocarbons. For example, TFE is similar in flammability to carbon monoxide. Also, TFE can explode in the absence of air to give carbon and carbon tetrafluoride. TFE shows the usual addition reactions of an olefin and will readily polymerize in the presence of free-radical initiators. Perfluorocyclobutane is formed slowly at room temperature and rapidly at 500°C (Sherratt, 1966).

Once the fluorocarbon monomers are polymerized into plastics, they exhibit a high degree of chemical stability. They are resistant to mineral acids, bases, and common organic solvents. The compounds are resistant to oxidation and ultraviolet radiation leading to good weathering properties. They are only attacked by alkali metals, fluorine, and strong fluorinating agents at elevated temperature and pressure. This stability is dependent upon the degree of fluorination in the monomer.

VIII. Biology

A. Absorption

The most common route of administration for the fluorocarbon gases involves absorption of compounds by plasma and/or red blood cells across the alveolar membrane. However, the ease of absorption from aveolar air is reported to be directly related to lipid solubility. Most common fluorocarbons, having a relatively low lipid solubility are not readily absorbed. Figure 1 illustrates this principle, showing the decrease in various fluorocarbon gases in static alveolar air plotted against duration of breath holding.

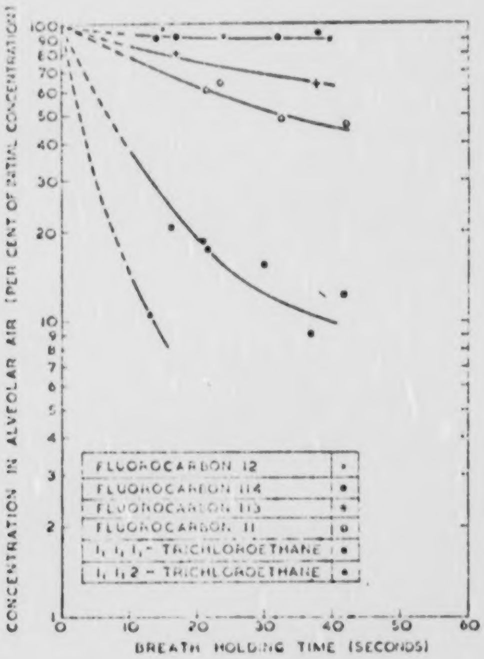

Figure 1. Concentration of Some Halogenated Hydrocarbons in Alveolar Air After Various Times of Breath Holding [Morgan *et al.*, 1972];
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Note that Fluorocarbon 12 [dichlorodifluoromethane] and Fluorocarbon 114 [1,2-dichlorotetrafluoroethane], both of which have low lipid solubilities, are only slightly absorbed. In contrast, the lipid soluble chlorocarbons are readily absorbed (Morgan _et al._, 1972). While this relationship may hold for the lower molecular weight fluorocarbons, hexafluorodichlorobutene has been reported 50% absorbed at a concentration of .1% over a one hour period (Truhant _et al._, 1972). Once into the blood stream, fluorocarbon absorption by the erythrocytes may be facilitated by the ionization of the polar gases and their subsequent binding to the positive and negative portions of the hemoglobin molecule (Pennington and Fuerst, 1971).

In that fluorocarbons are primarily used as gases or aerosol propellants, other routes of entry by absorption have not been extensively studied. Greenberg and Lester (1950) found no evidence for the absorption of 1,1,2,2-tetrachloro-1,2-difluoroethane or 1,1,1,2-tetrafluoro-2,2-difluoroethane through the gastrointestinal tract in rats. However, halothane ingestion by humans had lead to severe clinical pathology and death where gastrointestinal absorption would seem indicated (Dykes, 1970).

No studies monitoring the degree of dermal absorption have been encountered.

B. Excretion/Elimination

With the exception of unchanged and presumably unabsorbed fluorocarbons excreted in the feces after oral administration (Greenberg and Lester, 1950), fluorocarbons are removed from the body via exhalation and/or urinary excretion.

Removal of absorbed fluorocarbons by the respiratory tract has been well documented for aerosol propellants. In humans, over half of the absorbed doses of trichlorofluoromethane, dichlorodifluoromethane, trichlorotrifluoroethane, and 1,2-dichlorotetrafluoroethane are exhaled after 30 minutes representing a 77-90% elimination of the total administered dose (Morgan et al., 1972). Further elimination most probably continues for some time after the 30 minute period, in that rats have been shown to exhale 97% of administered trichlorofluoromethane unchanged over a 6 hour period (Cox et al., 1972a).

Fluorocarbon elimination by the respiratory tract is not merely coincident to inhalation administration, but also apparent after direct internal administration. A mixture of dichlorodifluoromethane and 1,2-dichlorotetrafluoroethane (30/70) injected intravenously and intraperitoneally or sprayed directly on an internal organ in dogs is not excreted by urine or feces but is eliminated by the breath. Table VII indicates that this elimination is of rapid onset and prolonged duration.

TABLE VII

Elimination of Fluorocarbons in Dogs' Breath
[Matsumoto et al., 1968]

	Intravenous	Intraperitineal	Direct Spray
Dosage	0.5 cc	2.0 cc	--
Interval before onset of elimination	3 sec.	5 min.	5 sec.
Duration of elimination	12 hours	48 hours	12 hours

Regretably, Matsumoto and associates (1968) did not report quantitative measurements of exhaled fluorocarbons. However, it is interesting to note that the four fold dosage increase in intraperitineal as opposed to intravenous injection leads to a corresponding four fold increase in the duration of fluorocarbon exhalation. This may indicate that the amount of a given fluorocarbon expelled by the respiratory system is independent of the administration route. The significant lag before respiratory elimination of the intraperitineal administration may reflect relatively poor membrane absorption characteristics of the fluorocarbons.

In contrast to the respiratory elimination of the aerosol propellants, the popular anesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) seems to undergo appreciable urinary excretion involving metabolic transformation (Geddes, 1972). After a single inhalation administration in man, halothane metabolites have been monitored in the urine for up to 14 days (Rosenberg, 1972). However, there is some evidence that considerable variation may be found in the proportions and rates of excretion by different individuals. Over a six day period, one individual excreted 85.7% of the original dose as urinary metabolites, while another excreted only 53.3% (Cascorbe and Blake, 1971). Many complex metabolic and renal parameters would have to be monitored before the significance of this variation could be assessed.

While most halothane studies have concentrated on urinary excretion, the role of respiratory elimination cannot be discounted. Clinical studies indicate that absorbed halothane may be eliminated by artificial ventilation with therapeutic results (Dykes, 1970). Similarly, the role of urinary excretion must also be considered in non-anesthetic fluorocarbons. Truhant and coworkers (1972) have shown that, while some hexafluorodicholobutene is eliminated in the breath after inhalation by rabbits, urinary excretion of the fluorocarbon metabolites is of major importance. Thus, no broad generalizations can be made on fluorocarbon excretion beyond the obvious fact that both the respiratory and urinary systems are involved. To what relative extents these systems are involved depends on the specific fluorocarbons. There is insufficient clinical and experimental data to clearly relate the physical or chemical characteristics of the fluorocarbons to the excretory pathways.

C. Transport

As should be obvious from the previous discussion on excretion, the main method of fluorocarbon transport within the organism is by the circulatory system. The compounds may be transported by the blood from the internal organs to the air way (Matsumoto _et al_.,1968) or from the air way to the urinary tract (Cascorbi and Blake, 1971; Geddes, 1972). However, fluorocarbons seem to be quickly eliminated from the blood stream (Beck _et al_., 1973). While the role of simple respiratory elimination is not to be minimized, there is considerable evidence - at least for halothane - that fluorocarbons may be transported by the circulatory system to the liver where they are removed from the blood (Rosenberg, 1972; Cascorbi and Blake, 1971; Cohen, 1969).

D. Distribution

Fluorocarbons being transported by the blood may be distributed for short periods throughout the organism. The primary site of fluorocarbon accumulation, however, seems to be the liver (Cascorbi and Blake, 1971). In the liver they accumulate as nonvolatile metabolites (Cohen, 1969). Trifluoroacetic acid is the metabolite most often cited--especially with reference to halothane--and may remain in the organism for up to two weeks (Waldron and Ratra, 1972). The metabolite itself may be stored in the fatty tissue and be gradually released and bound to the $-NH_2$ and -SH groups of peptides or proteins in the liver (Rosenberg, 1972).

E. Metabolism

Halothane, because of its importance as an anesthetic agent, has been the most intensively studied fluorocarbon in terms of metabolism. Trifluoroacetic acid (TFA) is recognized as the most probable end product of halothane metabolism in mammals and accounts for a large percentage of the urinary excretion (Blake *et al.*, 1972). This conclusion is supported not only by urinalysis but also by the similar metabolic effects of halothane and TFA (Stier *et al.*, 1972). Unlike the chlorocarbons which can be dehalogenated *in vivo* by enzyme systems, liberating chlorine ions and free radicals, the C-F bond is extremely stable and resistant to biological breakdown (Clayton, 1970). Thus with ^{14}C-labelled halothane, dechlorination and debromination do take place both *in vitro* and *in vivo* but no defluorination occurs. Labeled TFA is recovered as the end product (Geddes, 1972). Trifluoroethanol may be an intermediate in the formation of TFA in that up to 80% of ^{14}C-labelled trifluoroethanol may be recovered from the urine as TFA (Cascorbi and Blake, 1971). Although TFA seems to be the major metabolite, trifluoroacetylethanolamine and trifluoroacetaldehyde have been proposed either as end products or intermediates (Rosenburg, 1972). The current view of halothane metabolism is illustrated in Figure 2.

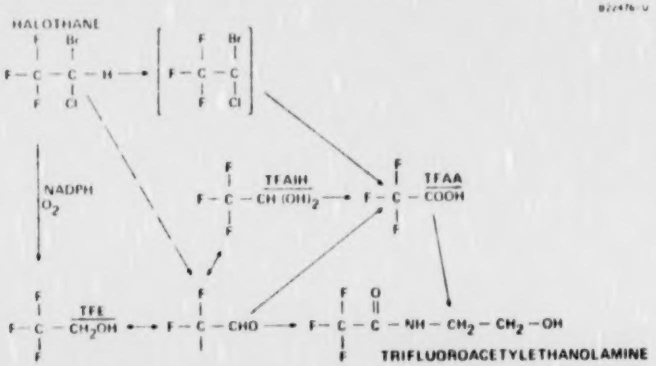


Figure 2: Possible Metabolic Pathways of Halothane
[from Rosenberg, 1972]

This general pathway or something similar to it may be common for a number of other fluorocarbons. Fluroxene (trifluoroethyl vinyl ether) may possibly be metabolized to trifluoroethanol in mice or TFA in man (Cascorbi and Singh-Amaranath, 1972). Hexafluorodichlorobutene may also be metabolized to TFA and other unidentified acids. This transformation may take place directly in the lung (Truhaut _et al._, 1972).

However, not all fluorocarbons can be assumed to follow this pattern. The one carbon compounds, of course, could not, and seem to operate by an entirely different mechanism. Trichlorofluoromethane does not undergo reductive dehalogenation in rat, mouse, chicken, hamster, or guinea pig microsomes and exhibits no evidence of free radical formation. It does not appear to undergo true biotransformation, but rather binds with hepatic cytochrome P-450 (Cox _et al._, 1972b).

The study of fluorocarbon metabolism is thus rather incomplete. The metabolic pathways assigned to halothane and related fluorocarbons are only tentative. The metabolism, if any, of the one carbon and many of the two carbon aerosol propellants is virtually unexplored.

F. Metabolic Effects

The metabolic effects of most fluorocarbons might be properly catagorized as cellular toxicity. However, in that most of the clinical and experimental results are documented only with lethality data or gross histopathology, the cellular and subcellular activity of these compounds can be examined apart from standard toxicity.

Halothane has been found to inhibit the replication of rat hepatoma cells, cells which usually multiply at a very rapid rate. Because the hepatoma cells were not in synchrony, a specific effect on a particular stage of the cell cycle could not be ascertained (Jackson, 1972). However, the effectiveness of halothane in reversibly dispersing a broad spectrum of microtubular systems has been extensively documented and is well reviewed by Nunn (1972). The inhibition of hepatoma growth observed by Jackson could well be accounted for by postulating a disruption of the mitotic spindle apparatus. Thus, while Jackson doubts the possibility of a common mechanism for growth inhibition and the inhibition of mycardial contractility, the universality of microtubular systems might allow for related mechanisms at least in terms of cardiac innervation (Nunn _et_ _al_., 1970). Until more is known about the nature of microtubular systems, however, such relationships must be considered highly speculative.

Beritic (1971) proposed that halothane may complex with mitochondrial elements. Such a complex may be involved in the _in_ _vitro_ uncoupling of oxidative phosphorylation in liver mitochondria (Snodgrass and Peras, 1965). A similar complex has been proposed for various fluorocarbons with cytochrome P-450 in liver microsomes uncoupling electron transport from monooxygenation (Ullrich and Diehl, 1971). Specifically, trichlorofluoromethane has been shown to bind hepatic cytochrome P-450 (Cox _et_ _al_., 1972a). In agreement with the lipophilic characteristics proposed by Ullrich and Diehl (1971), the hepatic binding involves phospholipids and also another area that appears similar to the carbon monoxide binding site (Cox _et_ _al_., 1972b). This is in further agreement with Ullrich and Diehl's (1971) characterization of fluorocarbons as "dead-end inhibitors". A similar type of enzymatic blockage has been proposed for fluoroacetate by the formation of fluoroacetyl-CoA. This would block the enzyme aconitase, cause an accumulation of citric acid, and a corresponding decrease in energy supply by way of the Kreb's Cycle (Peters, 1963). The effects of fluorocarbons on rabbit red blood cells *in vitro* may involve a somewhat related complexing by the ionization of the fluorocarbon and its binding to the positive and negative areas of the hemoglobin molecule (Pennington and Fuerst, 1971). To a greater or lesser extent, all of these observations are in accord with Nunn's hypothesis for fluorocarbon molecular activity: the biological activity of fluorocarbons is caused by Van Der Waal binding of the fluorocarbons to hydrophobic areas of large molecules (Nunn, 1972).

IX. Environmental Transport and Fate

A. Persistence and/or Degradation

The environmental stability of fluorocarbons has received little study. Information on biodegradability is not available. Goldman (1972) has reviewed the enzymology of carbon-halogen bonds and suggested that although fluorines substituted in the 2-position of short-chain fatty acids (e.g., fluoroacetate) are replaced by hydroxyl groups, the high strength of the carbon-fluorine bond would indicate a high biological stability. And, in fact, with any other compound containing the carbon-fluorine bond with the exception of fluoroacetate (e.g., trifluoroacetate, defluoroacetate, 2-fluoroproprionate, and 3-fluoroproprionate) fluoride release could not be detected.

Because of the volatility of many of the fluorocarbon compounds, atmospheric stability (chemical and photochemical inactivity) is likely to be quite important to the residence time of the chemical in the environment. Su and Goldberg (1973) have suggested that there is perhaps a similarity between stability in aerosol packages and thermal oxidative studies and in the atmosphere. Such a correlation seems to work for trichlorofluoromethane and dichlorodifluoromethane, with the more highly fluorinated compound being most stable as determined by monitoring data (see section on Chemical Reactivity).

Saltzman _et al._, (1966) have examined the atmospheric stability of bromotrifluoromethane and octafluorocyclobutane experimentally.

They determined the loss of the compound stored in bags exposed to ultraviolet irradiation, water, water vapor, and atmospheric pollutants with and without ultraviolet radiation. They concluded that their most significant loss was diffusion through the plastic bag.

Lovelock et al., (1973) and Su and Goldberg (1973) have calculated residence times for trichlorofluoromethane (10 years) and dichlorodifluoromethane (30 years) based on comparisons of world production levels and ambient air concentrations. These calculated values are quite dependent upon the sampling data used.

B. Environmental Transport

Atmospheric transport of fluorocarbons, especially the more volatile compounds such as trichlorofluoromethane, appears to be a very important route of environmental distribution. Lovelock (1972) has determined that trichlorofluoromethane contamination of south-west Ireland is due to sources on the European continent. He (Lovelock, 1973) has also shown a correlation of the ambient concentrations of trichlorofluoromethane in the environment and a numerical model of the global atmospheric distribution of an ideal inert gas.

C. Bioaccumulation

No experimental information on the bioaccumulation of fluorocarbons is available in the surveyed literature

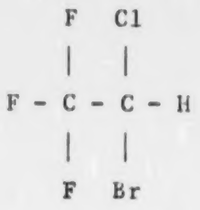
X. Toxicity

A. Human Toxicity

1. Acute Inhalation

The human clinical response to relatively high doses of fluorocarbon gases may be expressed in three ways: central nervous system depression, cardiac arrhythmias, and hepatic damage.

Depression of the central nervous system by fluorocarbons is reflected in their primary medicinal use, i.e., anesthetic. However, the actual degree of central nervous system depression varies considerably with the specific type of fluorocarbon and the concentration at which it is inhaled. The reactions may vary from slight loss of motor ability, to anasthesia, to convulsions (Azar et al., 1972). As a rule, fluorocarbons which contain more than four fluorine atoms are not useful anesthetics because at clinically effective doses they produce convulsions. If the fluorine number is increased to saturation, the compound becomes relatively inert. Thus, other halogens are often included in fluorocarbon anesthetics to decrease the adverse effects to an acceptable level without reducing the anesthetic potential (Clayton, 1970). Halothane is an excellent example of this type of fluorocarbon, containing only three fluorine atoms along with both chloro- and bromo- substitution:



$$\mathrm{F-\overset{\overset{F}{|}}{\underset{\underset{F}{|}}{C}}-\overset{\overset{Cl}{|}}{\underset{\underset{Br}{|}}{C}}-H}$$

Halothane

The cardiac effect of fluorocarbons on humans is less evident in cases of controlled medical administration then in instances of abusive inhalation of aerosol propellants by individual attempting to become intoxicated. As of 1972, one hundred and forty deaths had been attributed to such aerosol "sniffing" (Kilen and Harris, 1972). Most of these aerosol propellants are chlorinated fluorocarbons which have been shown to augment cardiac muscle response to epinephrine and induce irregular contractions leading to cardiac arrest (Clayton, 1970). In absence of definitive post-mortem findings, Reinhardt and associates (1971) proposed that the fluorocarbon propellants in the aerosol spray sensitized the heart to endogenous epinephrine -- which was released into the subjects blood stream by either physical activity or emotional stimulation -- leading to ventricular fibrillation and death. While not ruling out the scheme of indirect fluorocarbon toxicity via epinephrine, Taylor and coworkers (1971) proposed that the deaths might be accounted for on the basis of direct cardiac toxicity of the fluorocarbons. Noting that commonly used commercial products administered by fluorocarbon propellants may release from 38 ml to 231 ml of gas/sec and that bronchodilation nebulizers -- designed for direct inhalation -- may release 12.5 ml of gas/dose, they concluded that such products may present a serious threat (Taylor _et al._, 1971). The exact nature and extent of this danger has stimulated lengthy detailed experimentation on non-human mammals.

Compared to the chlorinated hydrocarbons, the fluorocarbons possess almost negligible hepatatoxicity (Clayton, 1970). However, the fluorocarbons do not seem to be entirely benign. Beritic and Dimov (1971) report that 1.02 out of 10,000 anesthetic administrations of halothane resulted in severe post-operative liver damage in 1967. Ether resulted in only 0.49: 10,000 cases of such damage. As yet, neither the extent of halothane involvement in these effects nor the possible mechanism for such involvement is clearly understood. Both direct hepatatoxicity and an immune response have been proposed (Beritic and Dimov, 1971). However, an _in vitro_ immune response could not be demonstrated in the lymphocytes of one group of 29 patients after halothane administration. Yet an immune response cannot be ruled out in an _in vivo_ system (Waldron and Ratra, 1972). Also, in that the incidence of liver damage is on the order of 1 in 10,000, a randomly selected group of 29 would not be expected to demonstrate the allergic mechanism even if such a a mechanism is involved in hepatotoxicity. No mechanism for direct liver damage has been postulated in the literature, but the various biological parameters previously outlined seem to deserve further investigation (Clayton, 1970).

2. Chronic Inhalation

Studies on long term low level inhalation of fluorocarbons are primarily concerned with occupational exposure to operating room personnel or workers in related situations. Recurrent hepatitis which lead to cirrhosis of the liver has been reported in an anesthetist (Beritic and Dimov, 1971). A low incidence of similar cases are summarized by Waldron and Ratra (1972). Of interest is a rare case of halothane liver damage which did show halothane induced lymphocyte stimulation. While this might indicate a form of allergic response, the sensitivity may be lost over relatively short periods of time. Similar studies using trichlorotrifluoroethane (113) indicated no toxic effects at a mean concentration of 699 ppm over an average of 2.77 years of occupational exposure (Imbus and Adkins, 1972). Female anesthetists have an increased rate of spontaneous abortions and the offspring show a higher incidence of congenital abnormalities, but the role of anesthetics has not been clearly assessed (Geddes, 1972). Halothane, at any rate does not seem teratogenic in vivo, causing no marked chromosomal damage in cultured human leucocytes (Nunn et al., 1971). Thus, although the chronic inhalation data for humans is hardly extensive, fluorocarbons seem to have a low order of toxicity but the development of individual hypersensitivity seems possible (Clayton, 1970)

3. Ingestion

Dykes (1970) has noted three cases of halothane ingestion, each in relation to a suicide or attempted suicide. In two cases, 250 ml were imbibed by a 48 year-old female and a 28 year-old male. Both survived, with the female first receiving medical attention 4½ hours after ingestion (the time before treatment commenced for the male was not specified). In the third case, a 19 year-old drank 35 ml of halothane and was found dead after 12 hours. This death is probably attributed to lack of prompt medical care. Cases of ingestion, however, are rare and are not likely to pose any wide-spread threat to human life.

4. Polymer-Fume Fever

Pyrolysis products of tetrafluoroethylene polymers (PTFE) have been recognized as having adverse effects on man since 1951. The disease is occupational and usually associated with smoking cigarettes that have been contaminated with PTFE dust. The response is characterized by tightness of chest, malaise, shortness of breath, headache, coughing, chills, elevated temperature and sore throat (Lewis and Kerby, 1965). The minimum one time dose is on the order of 0.40 mg PTFE (Clayton, 1970). The disease seems specific to man and cannot be reproduced in laboratory animals (Bischoff, 1972). The specific pyrolysis products responsible for polymer-fume fever have not been identified. Given the degradation products of PTFE over the 300-700°C range and the average temperature of 884°C for the burning zone of a cigarette, any of the following fluorocarbon products might be involved: octafluoroisobutylene, tetrafluoroethylene, hexafluoroethane, hexafluoropropylene, octafluorocyclobutane, or perfluoroisobutylene (Williams and Smith, 1972). The ill effects last for only a few days after removal of the causative agent (Lewis and Kerby, 1965).

B. Toxicity to Non-Human Mammals

1. Acute and Subacute Toxicity

The toxicity of the fluorocarbons may be discussed in terms of the various chemical groupings. The first of these, the fluoromethanes, illustrates well the basic characteristics of fluorocarbon toxicity. Table VIII indicates the toxicity levels for three groups of fluoromethanes.

TABLE VIII

Inhalation Toxicity of Fluoromethanes
[Clayton, 1970]

E X P O S U R E

Group	Structure	Concentration (%)	Time (hr)	Fatality	Class*	TLV**
A	$CHCl_3$	2.0	2	Yes	3	50
	$CHCl_2F$	10.0	1	Yes	4-5	1000
	$CHClF_2$	20.0	2	No	5a	(1000)
	CHF_3	20.0	2	No	6***	(1000)
B	CCl_4	2.0	2	Yes	3	10
	CCl_3F	10.0	2	No	5a	1000
	CCl_2F_2	20.0	2	No	6	1000
	$CClF_3$	20.0	2	No	6***	(1000)
	CF_4	20.0	2	No	6***	(1000)
C	CH_3Cl	2.0	2	Yes	4	100
	CH_2Cl_2	5.0	2	Yes	4-5	500
	$CHCl_2F$	10.0	1	Yes	4-5	1000
	CCl_2F_2	20.0	2	No	6	1000

*Classified according to Underwriters' classification. The higher the value the lower the toxicity.

**TLV, threshold limit value assigned by the American Conference of Governmental Industrial Hygienists, 1968 values. Figures in parentheses indicate provisional values.

***Based on data from Haskell Laboratory.

As a rule, the toxicity decreases as the number of fluorine atoms increases. Chemically, the decrease in toxicity may be seen as an increase in the stability of the molecule due to fluorine substitution (Clayton, 1970). The above data, in that it indicates only lethal doses, might be considered only a rough criteria by which to compare toxicity. However, the detailed studies of Lester and Greenberg (1950) over a wide range of responses bear out the above generalization. The effect of trichlorofluoromethane and dichlorodifluoromethane on rats for 1/2 hour exposure periods at various concentrations are indicated in Table IX.

TABLE IX

Dose/Effect Relationship for CCl_2F_2 and CCl_3F
[Lester and Greenberg, 1950]

	% CCl_2F_2 in air	% CCl_3F in air
No effect	20-40	5
Mild Intoxication	50	6-7
Moderate Intoxication	60	8
Unconsciousness	70-80	9
Mortality	-	10

The relationship seems to hold not only for the effect on the central nervous system, but also for the sensitization of the heart to epinephrine. Table X shows the response of beagle dogs exposed to various concentrations of $CHClF_2$, CCl_2F_2, CCl_3F over a five-minute interval.

TABLE X

Cardiac Sensitization to Epinephrine
[Reinhardt et al., 1971]

Compound	Conc. (%)	% Sensitization
CCl_3F	1.21	41.3
CCl_2F_2	5.0	41.7
$CHClF_2$	5.0	16.7

From this study it might also be tempting to assume not only that toxicity decreases with the number of fluorine atoms but also that it increases with the number of chlorine atoms [a standard assumption in simple chlorocarbon toxicity]. However, biological systems do not readily lend themselves to firm rules. Note from Table X (Clayton, 1970) that $CHCl_2F$ is significantly more toxic than CCl_3F. For this specific case, the significantly higher dipole moment for $CHCl_2F$ (1.293) over CCl_3F (0.45) might result in an increased ability of $CHCl_2F$ to bind to the positive and negative areas of macromolecules similar to the effect noted by Pennington and Fuerst (1971).

The bromine substituted fluorocarbons seem to behave much the same as the chloroderivatives with respect to the influence of fluorination on toxicity, but the data obtained thus far is severely limited. Only two compounds have been compared in this survey: bromotrifluoromethane ($CBrF_3$) and bromochlorodifluoromethane ($CBrClF_2$). At concentrations of 5.0% - 30.0%, $CBrClF_2$ has been shown to have marked central nervous system and cardiac effects on rats, mice, guinea pigs, dogs, and a monkey. The neurologic effects included initial stimulation, tremors, convulsions, and eventual CNS depression leading to death. The cardiac effects entail a decrease in the force of contraction and a sensitization to epinephrine induced arrhythmias (Beck _et al._, 1973). At comparable concentrations, 10.5% - 42%, $CBrF_3$ leads to some decrease in performance of pre-conditioned tasks in monkeys but no central nervous system damage (Carter _et al._, 1970). This is similar to the minor effects noted in man at concentrations of 7% (Call, 1973). At a concentration of 30% [which caused the most severe damage using $CBrClF_2$], $CBrF_3$ did cause mild to moderate hypotension with some indication of arrhythmias and a slight decrease in neural response in cats (Greenbaum _et al._, 1972). At concentrations of 80%, there was a reversible decrease in neural inhibition of the heart and evidence of significant general neural suppression (Van Stee and Back, 1972). Thus, while both $CBrClF_2$ and

$CBrF_3$ are capable of demonstrating neural and cardiac toxicity, $CBrF_3$ seems appreciably less potent. To what extent this is caused by an increase of a fluorine atom as opposed to the absence of the chlorine cannot be determined without more data.

The overall effect of bromination as compared to chlorination on the methane series also cannot be clearly determined. Detailed data is available on only one set of comparable compounds, CCl_2F_2 and $CBrClF_2$. At concentrations of 30% over 30 minutes to rats, $CBrClF_2$ has a much more deliterious effect on cardiac and neural tissue (Beck _et al._, 1973) than the relatively mild muscular twitching caused by CCl_2F_2 (Lester and Greenberg, 1950). Yet this data does not seem sufficient to warrant any generalization.

The toxicity of the fluoroethanes is similar to that of the methanes in that an increased number of fluorine atoms tends to decrease the toxicity. Table XI illustrates this progression for a series of two to six fluorine atom molecules (Clayton, 1970).

TABLE XI

Acute Inhalation Toxicity of Several Fluoroethanes [modified from Clayton, 1970]

#F	Structure	ALC(%)*	Exposure (hr)	Animal
2	CCl_2F-CCl_2F	1.5	4	Rat
2	$CClF_2-CCl_3$	1.5	4	Rat
3	$CHCl_2-CF_3$	3.5**	4	Rat
3	$CCl_2F-CClF_2$	10.0	4	Rat
4	$CClF_2-CHF_2$	>20.0	2	Guinea Pig
4	$CClF_2-CClF_2$	>20.0	8	Guinea Pig
5	CHF_2-CF_3	>10.0	4	Rat
5	$CClF_2-CF_3$	>80.0***	4	Rat
6	CF_3-CF_3	>80.0***	4	Rat

*ALC, approximate lethal concentration, a reliable estimate of LC_{50}

**LC_{50}

***Fluorocarbon, 80%; oxygen, 20%.

A steady decrease is seen along the series with the unexplained exception of CHF_2-CF_3. However, equally important, a consistent hydrogen/chlorine effect seems evident. For the two compounds in the three, four, and five series, the only difference is a hydrogen in place of a chlorine atom. In each case, the hydrogen compound is appreciably more toxic. This may relate to the previously noted greater toxicity of $CHCl_2F$ over CCl_3F. The data presented for the two fluorine atom series shows no variation in a fluorine/chlorine substitution. Similar studies on the same two fluorocarbons by Greenberg and Lester (1950) proved similarly inconclusive. CCl_2F-CCl_2F at 0.5% caused death as early as 4 hours and as late as 36 hours. CCl_3-CClF_2 at 2.0-3.0% caused death in 1-2 1/2 hours. Thus both evidence about the same degree of toxicity. However, in another series of compounds, CH_3-CHF_2 and CH_3-$CClF_2$, the chlorine again causes an apparent decrease in toxicity (Lester and Greenberg, 1950). CH_2-$CClF_2$ caused death in rats at 50%-80% over a 30 minute period. CH_2-CHF_2 caused death in rats at 50%-55% over a 10 to 25 minute period. Consequently, it seems clear that hydrogen substitution of chlorine may significantly increase the toxicity of chlorofluorocarbons.

The general decrease in toxicity with increased fluorination seems valid not only for acute inhalation but also for cardiac sensitization. In the beagle dog over a five minute period of exposure, 5.0% ClF_2C-CF_2Cl caused 58.3% sensitization. Under the same circumstances, 25% ClF_2C-CF_3 caused only 33.3% sensitization (Reinhardt et al., 1971).

The effect of bromination as opposed to chlorination is indicated in Table XII.

TABLE XII

Comparison of Bromine and Chlorine in the Acute Inhalation Toxicity of Fluoroethanes [Clayton, 1970]

Compound	Lethal Concentration* (% by volume)
CH_2Cl-CF_3	25.0
CH_2Cl-CHF_2	7.5
CH_2Br-CF_3	11.7
CH_2Br-CHF_2	4.6

*Mice were exposed for 10 minutes.

The substitution of bromine for chlorine decreases the toxicity of fluoroethanes. This effect may be additive in that the lethal concentration for CH_2Br-$CBrF_2$ is 1% as opposed to 4.6% for CH_2Br-CHF_2 (Lester and Greenberg, 1950).

The effect of fluorination on fluoroethylenes is by no means clear. Clayton (1970) summarizes data presented in Tables XIII and XIV indicating that increased fluorination may increase toxicity.

TABLE XIII

Inhalation Toxicity of Several Fluoroalkenes
[Clayton, 1970]

		Acute Toxicity for Rats* (ppm)	
Structure	No. of F Atoms	ALC	LC_{50}
$CH_2 = CHF$	1	> 800,000**	
$CF_2 = CH_2$	2	128,000 > 800,000***	
$CF_2 = CF_2$	4		40,000
$CF_3\text{-}CF = CF_2$	6		3,000
$(CF_3)_2 = C = CF_2$	8	0.5, 0.76****	

*Exposures are for 4 hour duration except where noted. ALC, approximate lethal concentration. LC_{50}, lethal concentration for 50% of rats exposed.
**$CH_2 = CHF$, 80%; O_2, 20%; 12.5 hour exposure.
***$CH_2 = CF_2$, 80%; O_2, 20%; 19 hour exposure.
****Exposure at 0.5 ppm, 6 hour; at 0.76 ppm, 4 hour.

TABLE XIV

Inhalation Toxicity of Several Halogenated Alkenes
[Clayton, 1970]

	No. of Atoms		Acute Toxicity for Rats* (ppm)	
Structure	F	Cl	ALC	LC_{50}
$CCl_2 = CH_2$	0	2	32,000	
$CHCl = CCl_2$	0	3	8,000	
$CCl_2 = CCl_2$	0	4	4,000	
$CCl_2 = CF_2$	2	2	1,000	
$CClF = CF_2$	3	1		1,000

*Exposures of 4-hour duration. ALC, approximate lethal concentration. LC_{50}, lethal concentration for 50% of rats exposed.

Clayton (1970) proposes that the toxicity of these compounds may be affected primarily by the double bonds rather than the degree of fluorine substitution. While this may hold true for structurally dissimilar compounds, there is some indication that closely related compounds do show a decrease in toxicity with increased fluorination. Lester and Greenberg (1950) found that at concentrations of 80% and exposure periods of 30 minutes $CH_2=CF_2$ had a noticeably less toxic effect on rats than did $CH_2=CHF$. This agrees with the data presented by Clayton (1970) indicating that 80% $CH_2=CF_2$ required 6.5 more hours of exposure than did 80% $CH_2=CHF$ to elicit an acute toxic response in rats. The relative paucity of experimental data prevents productive comparison of the fluoroethanes with the fluoroethylenes.

Certain fluorinated butylenes have been studied in some detail and found to be highly toxic. Beritic and Dimov (1971) have cited 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2[DCHFB] as a 180-300 ppm contaminant in halothane. This highly toxic compound has been suspected of causing the hepatotoxic response to halothane (Clayton, 1970). Toxicity data on DCHFB is summarized in Table XV.

TABLE XV

LC_{50} for DCHFB

[Truhaut et al., 1972]

	LC_{50} (1 hr.)	LC_{50}(3 hr.)	LC_{50} (4 hr.)
Rats	100 ppm	50 ppm	16 - 100 ppm
Mice	61-75 ppm		26 ppm
Dogs		200 ppm	182 ppm
Monkeys		90 ppm	
Rhesus		54 ppm	

Although DCHBF has been shown to cause liver damage (Clayton, 1970), Truhaut and coworkers (1972) showed that the liver function was usually normal in fatally intoxicated rabbits (Table XVI). This seems to agree with the low incidence of "halothane hepatitis", 1:10,000. The prime characteristic is a delay in lethality similar to that noted for 1-chloro-1,2,2-trifluoroethylene (Walther et al., 1970).

TABLE XVI

Delayed Death After DCHFB Administration to Rabbits
[Truhaut et al., 1972]

Concentration Exposure time	500 ppm 1 hour	200 1 hour	100 1 hour	200 30 minutes	200 15 minutes
Delayed Death	85 min. to 3 1/2 hours	12 hours	4 days	3 days	0

Such a delay indicates that a metabolite such as trifluoroacetic acid rather than the parent compound may be the toxic agent (Truhaut et al., 1972).

As can be seen from Table XIII, perfluoroisobutylene (PFIB) is the most toxic of the fluoroalkenes cited. However, with the exception of Clayton's brief summary (Clayton, 1970), no studies on this compound were encountered in the literature.

2. Chronic Toxicity

Fluorocarbon toxicity has been studied primarily as an acute response. Chronic data is scarce but a very low level of chronic toxicity seems indicated. This is to be expected given the body's apparent ability to excrete fluorocarbons. Table XVII summarizes experimental work showing essentially no pathology with chronic levels of exposure.

TABLE XVII

Chronic Exposure to Some Fluorocarbons Showing No Pathology

Compound	Animal	Concentration	Exposure
CCl_3-$CClF_2$*	Rat	0.1%	18 hr/day x 17 days
CCl_2F-CCl_2F*	Rat	0.1%	18 hr/day x 16 days
CCl_2F-CCl_2F**	Mice, Guinea Pig, Rabbit	0.1%	6 hr/day x 30 days
CH_3-$CClF_2$***	Rat	1.0%	16 hr/day x 60 days
CH_3-CHF_2***	Rat	10.0%	16 hr/day x 60 days

*Greenberg and Lester, 1950.
**Clayton *et al.*, 1964.
***Lester and Greenberg, 1950.

The only positive chronic toxicity was obtained with the exposure of rats to 0.1% CCl_2F-CCl_2F for 6 hr/day x 30 days. A slight decrease in leucocytes in the peripheral blood was noted along with lung irritation and unspecified histologic changes in the liver (Clayton *et al.*, 1964).

While the above studies do deal with chronic exposures in comparison to other fluorocarbon studies, it must be noted that the concentrations are extremely high and the exposure period correspondingly short with reference to environmentally meaningful studies.

3. Sensitization

There is clear evidence that some humans may become sensitized to to halothane exposure (Beritic and Dimov, 1971) and similar sensitization might be expected in other mammals. Nevertheless, halothane itself has not been shown to act as a partial antigen in rats and is probably not responsible for the sensitization Since unidentified trifluoropeptides do accumulate in the liver and circulate in the blood, Rosenberg (1972) proposes that fluoroacetaldehyde may combine with mitochondrial proteins thus causing an auto-immune response.

In the only other sensitization study encountered, 1,1,2,2-tetrachloro-1,2-difluoroethane did not produce skin sensitization in guinea pigs (Clayton _et_ _al_., 1964).

4. Teratogenicity

As noted in the discussion of human toxicity, halothane has been shown to be a reversible mitotic spindle poison (Nunn et al., 1971). Such compounds must always be considered potential teratogens due to possible non-disjunction if not actual chromosomal damage. However, in the absence of experimental data, the teratogenic effect - if any - of halothane or any other fluorocarbon is speculative at best.

5. Carcinogenicity

Fluorocarbons alone have not been implicated as carcinogenic agents. However, fluorocarbons - particularly tetrachlorodifluoroethane(112) - in conjunction with piperonyl butoxide has been shown to be hepatocarcinogenic in mice (Epstein _et_ _al_., 1967). As indicated in Table XVIII, neither compound alone shows appreciable carcinogenicity.

Similar follow up studies have not been encountered, thus the significance of this study is difficult to evaluate. However, the possibility of synergistic behavior of the fluorocarbons with other environmental compounds should be an area of future investigations.

6. Mutagenicity

No studies on fluorocarbon mutagenicity have been encountered.

7. Behavioral Effects

Intoxication and anesthesia might be considered behavioral effects but these are amply discussed under toxicity studies.

TABLE XVIII

Tumors Induced in Swiss Mice by Injection of "Freons"
and Piperonyl Butoxide Shortly After Birth
[from Epstein et al., 1967]

Treatment Group	Sex	No. of mice, subsequently autopsied, alive at the beginning of each period (No. at risk)					No.	Hepatomas No. tumors in each period as % of No. of mice at risk				No.	Malignant lymphomas No. tumors in each period as % of No. of mice at risk			
		Weeks						Weeks					Weeks			
		11-20	21-30	31-40	41-50	51+		21-30	31-40	41-50	51+		21-30	31-40	41-50	51+
Solvent controls	M	72	68	59	55	48	4	0	0	0	8	1	0	0	0	2
	F	69	69	69	68	68	0	0	0	0	0	0	0	0	0	0
"Freon" 11	M	25	25	22	21	21	2*	0	0	0	10	1	4	0	0	0
	F	20	20	20	20	20	0	0	0	0	0	0	0	0	0	0
"Freon" 112	M	27	27	27	20	17	0	0	0	0	0	0	0	0	0	0
	F	22	22	21	20	19	0	0	0	0	0	0	0	0	0	0
"Freon" 113	M	29	29	29	26	21	1	0	0	0	5	0	0	0	0	0
	F	21	21	20	20	20	0	0	0	0	0	1	0	0	0	5
Piperonyl butoxide	M	40	38	35	25	20	0	0	0	0	0	0	0	0	0	0
	F	36	36	36	36	36	0	0	0	0	0	0	0	0	0	0
"Freon" 112 and piperonyl butoxide	M	30	26	26	14	13	5	0	0	7	31	0	0	0	0	0
	F	29	29	28	25	24	0	0	0	0	0	3	0	4	0	8
"Freon" 113 and piper onyl butoxide	M	25	24	24	19	18	3	0	0	0	17	0	0	0	0	0
	F	24	24	24	24	24	0	0	0	0	0	1	0	0	0	4

* One of these also had a pulmonary adenoma.

C. Toxicity to Lower Animals

No studies of fluorocarbon toxicity to the lower animals have been encountered.

D. Toxicity to Plants

Halothane has been shown to cause metaphase arrest in the root tips of *Vicia faba*, the European broad bean. The ED_{50} ranges from 0.5-0.9%. Total arrest is achieved with 2.0% over 8 hours (Nunn *et al.*, 1971). Although fluoroacetate can be accumulated by some plants (Peters, 1963), there is no evidence that it is the result of fluorocarbon metabolism.

E. Toxicity to Microorganisms

Similar to its effect in *Vicia faba* (Nunn *et al.*, 1971), halothane has been shown to cause reversible microtubular disruption at 2% concentration over a 7 minute period in *Actinosphaerium nucleofilum*, a heliozoan protozoa (Allison *et al.*, 1970).

Halothane and chlorodifluoromethane have both been shown to decrease the bio-luminescence of *Photobacterium phosphoreum* (White and Dundas, 1970). The effect of halothane is shown in detail in Figure 3.

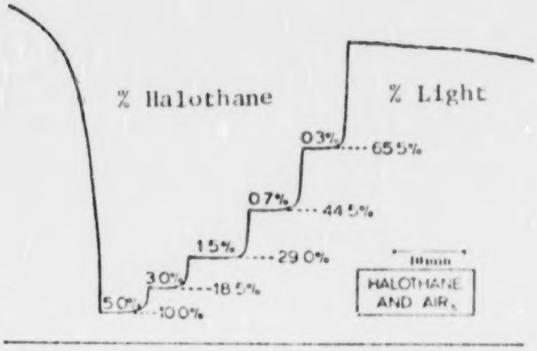


Figure 3: Effect of Halothane on Bioluminescence of *P. phosphoreum* [from White and Dundas, 1970]

This effect occurs at concentrations comparable to those causing anesthesia in mice (Halsey and Smith, 1970). Dichlorodifluoromethane and 1,1-difluoro-1-chloroethane were both found to be toxic to a wide variety of microorganisms in liquid but not in vapor stages (Prior *et al.*, 1970).

While these few studies do not allow for broad generalizations, they do indicate that at least some microorganisms respond to certain fluorocarbons at comparable concentrations causing physiological responses in higher life forms.

XI. Fluorocarbons: Summary and Conclusions

Fluorocarbons are an obvious and growing source of environmental contamination. An annual production of nearly one billion pounds may be reached in the next decade. Of this production, over half will be directly released into the environment as aerosol propellants, solvents, or refrigerant leakage. The specific types and relative order of fluorocarbon discharge will probably be dichlorodifluoromethane > trichlorofluoromethane > chlorodifluoromethane >> dichlorotetrafluoroethane > trichlorotrifluoroethane. The two more common of these (dichlorodifluoro- and trichlorofluoromethane) have already been monitored in the environment at background concentrations below 1 ppb. The fluorocarbon plastics, while not used in high turnover products, will eventually enter the environment either intact or as pyrolysis products in millions of pounds per year amounts. Proposed new uses for the fluorocarbons (e.g. food freezing and dry cleaning) may provide high exposure potentials similar to present uses.

Under normal environmental conditions, all of the fluorocarbons will probably show a marked degree of persistance. The C-F bond is highly stable and biological reductive defluorination does not seem likely. Although precise estimates of persistance are not yet possible, residence times on the order of 10-30 years do not seem improbable. Monitoring information thus far available on dichlorodifluoromethane and trichlorofluoromethane indicates that the actual and theoretical orders of fluorocarbon persistance may be in agreement. Taking into account both production and persistance, a total environmental load of five billion pounds may well be a conservative estimate.

Usage and monitoring data both indicate that the fluorocarbons will be primarily distributed in areas of high population or production. By far the greatest amount of fluorocarbon release will be consumer based from aerosol sprays. Dwellings are likely to contain significantly greater amounts (hundreds of ppb) than the ambient air. Obviously, the air is the most probable mode of transport with the fluorocarbon concentration constantly moving toward equilibrium. Thus, as fluorocarbon use proceeds, background levels in populated and nonpopulated areas are likely to increase steadily, while levels inside of dwellings will fluctuate widely depending on the amount of fluorocarbons used.

Although the likelihood of fluorocarbon release into the environment in increasingly large amounts is well documented, the hazards posed by such contamination are ill-defined. Cases of aerosol abuse, polymer-fume fever, and halothane hepatitis are primarily medical problems and have little, if any, environmental relevance. Mammalian systems do not seem to exhibit any toxic response in chronic exposures to the commercially important fluorocarbons at concentrations as high as 100,000 ppm. Microbial organisms exhibit a similar degree of fluorocarbon resistance. However, not enough is known of the biological behavior of these compounds to rule out long-term occult pathogenesis. There are reasonable indications that fluoromethanes may bind tightly to biologically important macromolecules. This has been shown to result in metabolic interference and may also be used to postulate possible mechanisms for biological accumulation and magnification. Further, plants and non-mammalian animals have not been extensively studied for fluorocarbon toxicity. If macromolecular binding is a reasonable possibility, population decreases and reduced viability of these organisms might be a good indicator of fluorocarbon hazard.

Fluorocarbons, like any foreign substances that are released in the environment in large amounts, are potential environmental poisons. Although these compounds do not seem to represent an immediate danger, a steady increase in environmental concentrations may be expected. Where the danger threshold is cannot be determined without further study. Present "chronic" toxicity data are given in terms of hundreds of days. Such information has limited environmental application. Study periods based on the half life of important organisms would be more helpful. One point, however, seems relatively certain. If toxic concentrations are reached before the danger threshold is set, ecological havoc is likely to ensue. Fluorocarbons are both plentiful and persistant. These factors alone would seem to warrant a more precise definition of their environmental toxicity.

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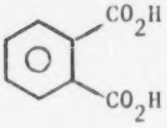
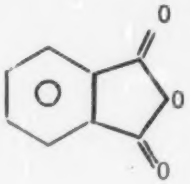
BENZENEPOLYCARBOXYLATES

(Acids, Anhydrides, and Salts)

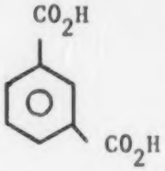
Because of their commercial importance, this report will focus on the following chemical commodities:



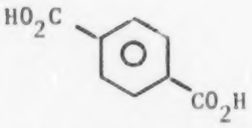
phthalic acid
(PA)



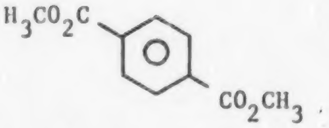
phthalic anhydride
(PAN)



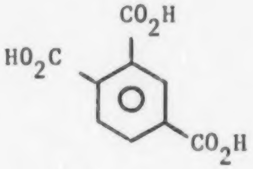
isophthalic acid
(IA)



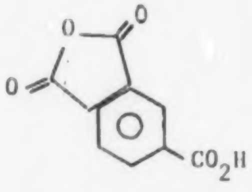
terephthalic acid
(TA)



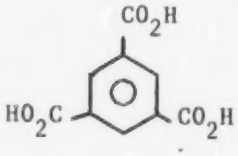
dimethyl terephthalate
(DMT)



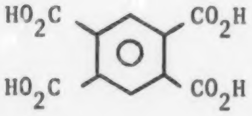
trimellitic acid
(TMA)



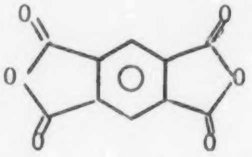
trimellitic anhydride
(TMAN)



trimesic acid
(TMSA)



pyromellitic acid
(PMA)



pyromellitic dianhydride
(PMDA)

Dimethyl terephthalate was included with terephthalic acid because they are virtually inseparable so far as their major applications are concerned.

I. Physical Properties

The benzenepolycarboxylate compounds are generally crystalline white or colorless solids at ambient temperatures. Terephthalic acid is the most insoluble in water and has the highest melting point of all the benzenecarboxylic acids. The high melting point makes it a difficult material to purify. Therefore, the lower melting dimethyl ester is often used as a source of terephthalate.

The physical properties of the anhydrides are dependent upon the equilibrium constant of the reaction: Anhydride + $H_2O \rightleftarrows$ Acid. Of course, anhydrides are only formed in compounds that contain acid functions ortho to each other (PA, TMA,PMA). Phthalic anhydride at room temperature is relatively stable, while trimellitic anhydride will react with water vapor to form the acid.

Physical constants for some of the benzenepolycarboxylates are listed in Table 1.

TABLE I

Physical Properties of Commercially Important Benzenepolycarboxylates
(Towle et al., 1968)

Property / Compound	PA	PAN	IA	TA	DMT	TMA	TMAN	TMSA	PMA	PMDA
Boiling point °C		284.5			288		390			397-400
Melting point (dry air) °C	191	131	345		140	216-218	168	375-380 (sublimes)	257-265 (decomp.)	287
Specific gravity or density		1.527	1.507	1.510 g/ml						1.68
Sublimation point °C				402						
Ionization Constant First Second	 1.1×10^{-3} 5.5×10^{-6}		 3.3×10^{-4} 3.2×10^{-5}	 3.1×10^{-4} 1.5×10^{-5}		 3.0×10^{-3} 1.4×10^{-4}		 7.4×10^{-4} 1.3×10^{-4}	 1.20×10^{-2} 1.29×10^{-3}	
Vapor pressure (mmHg)		6 (132°C)		0.5 (120°C)	10 (141°C)		2 (200°C)			
Solubility g/100g solvent										
H_2O	0.54 (14°C)	0.62 (25°C)	0.013 (25°C)	0.0019 (25°C)		2.1 (25°C)	reacts	0.24 (25°C)	1 (20°C)	
glacial ACOH	12.0 (100°C)		0.078 (25°C)	0.035 (25°C)						
methanol or ethanol	11.7(e) (18°C)		2.1(m) (25°C)	0.1(m) (25°C)	1.0(m) (25°C)	25.3(e) (25°C)	reacts	8.0(m) (25°C)	10(e) (10°C)	
Hydrocarbon solvent			insol. (benzene)		2.0 (benzene)	0.006 (xylenes)	0.4 (xylenes)	<0.01 (o-xylene)		
halogenated solvent					1.5 CCl_4(25°C)	0.004 (CCl_4)	0.002 (CCl_4)	<0.01 (CCl_4)		

II. Production

Of the benzenepolycarboxylates, the disubstituted acids and anhydrides are the most important commercially. Terephthalic acid, the dimethyl ester of terephthalic aicd, and phthalic anhydride are produced in the largest quantities. Table II presents the available production figures for the various benzenecarboxylates. Lack of information on the trimellitic acid production required the substitution of ester production figures. The quantity of trimellitic acid produced will be somewhat smaller than the ester production due to the increase in molecular weight of the ester product (assuming relatively high reaction yields).

The capacities and plant locations of major producers of benzenepolycarboxylates are listed in Table III. A variety of manufacturers and production sites are involved in the manufacture of these chemicals.

TABLE II

Production of Benzenepolycarboxylates
(U.S. Tariff Commission, 1961-1971; Towle _et al._, 1968, Blackford, 1970)

	PAN		IA		DMT		TA		Trimellitic Acid Esters		Polyimide Polymers (TMAN and PMDA based)	
	10^9g	10^6 lbs	10^9g	10^6 lbs	10^9g	10^6 lbs	10^9g	10^6 lbs	10^9g	10^6 lbs	10^9g	10^6 lbs
1961	172	380	20	45	32*	70*						
1962	194	427	25	55	29*	65*						
1963	208	459	27	60	150	331			0.40	0.88		
1964	253	558	29	65	161	356			0.52	1.14	0.11	0.25
1965	276	608	32	70	247	545			0.90*	1.98*		
1966	306	675	34	75	362	797	233	514	1.15	2.54		
1967	330	727	39	85	425	936	315	694	2.84	6.25		
1968	337	744	43	95	594	1,309	420	927	2.15	4.73		
1969	345	760	43	95	697	1,537	474	1,045	3.42	7.55		
1970	333	734			656	1,447	603	1,329	4.40	9.70		
1971p	360	794			789	1,739	718	1,582	5.14	11.34		

*Sales

TABLE III

Capacities for Production of Benzenepolycarboxylates

Phthalic Anhydride
(Erskine, 1970; Chemical Marketing Reporter, 1972)

Producer	Plant Capacity (million lbs.)	Plant Location
Allied Chemical Co.	135	El Segundo, Calif. Frankford, Pa.
	40 (not operating)	Ironton, Ohio
BASF Wyandotte	130	South Kearney, N.J.
Chevron Chemical Co.	50	Richmond, Calif.
Enjoy Chemical Co.	90 (in start-up procedure)	Baton Rouge, La.
W.R. Grace & Co.	75 (on stand-by)	Fords, N.J.
Koppers Company, Inc.	220	Bridgeville, Pa. Chicago, Ill.
Monsanto Company	210	Bridgeport, N.J. Texas City, Tex.
Puerto Rico Chemical Co. (Hooker Chem. Corp.)	100	Arecibo, Puerto Rico
Reinhold Chemicals, Inc.	130 (uncertain of status)	Elizabeth, N.J. Morris, Ill.
Sherwin Williams Chemicals	20 (uncertain of status)	Chicago, Ill.
Stepan Chemical Co.	48	Millsdale, Ill.
Union Carbide Corp.	100	Institute, W. Va.
United States Steel Corp.	125	Neville Island, Pa.

Isophthalic Acid
(Towle *et al.*, 1968; Blackford, 1970)

Chevron Chemical Co.	35 (closed, 1967)	Richmond, Calif.
Amoco Chemicals Corp.	88	Joliet, Ill.
Atlantic Richfield Co.	35	Channelview, Tex.

Dimethyl Terephthalate and Terephthalic Acid
(Frey, 1970; Chemical Marketing Reporter, 1973)

Amoco Chemicals Corp.	900 220 (DMT and TA)	Decatur, Ala. Joliet, Ill.
E.I. DuPont de Nemours & Co., Inc.	300 250 450 (DMT only)	Gibbstown, N.J. Old Hickory, Tenn. Wilmington, N.C.
Eastman Kodak Co. (Tennessee Eastman Co.)	350 (DMT only)	Kingsport, Tenn.
Hercules, Inc.	150 (DMT only) 850 (DMT and TA)	Burlington, N.J. Wilmington, N.C.
Hoechst Fibers	150 (DMT only)	Spartanburg, S.C.
Mobil Chemical Co.	150 (TA only)	Beaumont, Tex.

Trimellitic Anhydride
(Towle *et al.*, 1968)

Amoco Chemicals Corp.	50	Joliet, Ill.

III. Uses

Benzenepolycarboxylic acids are important organic intermediates in the plastics industry. They are used to synthesize plasticizers, alkyd resins, and condensation polymers of various types, polyesters and polyamides being the most common. These polymers are used in the production of fibers, film, surface coatings, and molding polymers. The following discussion is divided into sections for the commercially important isomers.

A. Phthalic Acid (PA) and Phthalic Anhydride (PAN)

Air oxidation of naphthalene or σ-xylene produces phthalic anhydride, which is the form utilized in the preparation of secondary products. The major outlet for phthalic anhydride is in the production of diesters of monohydric aliphatic alcohols for plasticizers, as can be seen in Table IV.

TABLE IV

Phthalic Anhydride Consumption-1968
(Erskine, 1970)

Use	Quantity (10^6 lbs)
Plasticizers	364
Alkyd resins	193
Unsaturated polyester resins	95
Exports	21
Miscellaneous	90
	763

The largest volume product is the di(2-ethylhexyl)ester (DEHP). DEHP and other diisooctyl and diisodecyl esters ("iso" means highly branched in the plasticizer industry) are used in applications where low temperature properties and low volatility are important. The more volatile low molecular weight esters are used for polar polymers like polyvinylacetate and cellulosics. The low price and flexibility of the phthalate plasticizers suggests that they will continue to be the most commonly used plasticizer growing at a rate of 8-10% per year (Erskine, 1970).

Up until 1960, the use of phthalic anhydride in alkyd resins was the major application. However, since that time, consumption of phthalic anhydride for plasticizers has far exceeded consumption for alkyd resins due to a relatively slow growth in alkyd resin demand. Alkyd resins are produced by reacting polybasic acids or anhydrides with polyhydric alcohols (e.g. glycerin and pentaerythritol). These products are usually modified by inclusion of drying oils, nondrying oils, semidrying oils, natural resins, or acids from natural resins. These resins impart to the finished coating such properties as outstanding weather and exposure resistance, flexibility, and excellent adhesion to the surface to be protected.

The third largest use of PAN is in the preparation of unsaturated polyesters. These are prepared by combining PAN, a glycol, and an unsaturated acid or anhydride (usually fumaric acid or maleic anhydride). This application represents the most dynamic and fast-growing end use of PAN. A large portion of these polyesters are used for structural building parts such as in corrugated sheet and in boat hulls.

Another major use of PAN is in the preparation of various classes of dyes and various chemical intermediates. Table V lists some of these dyes and intermediates.

TABLE V

Intermediates and Dyes Produced from Phthalic Anhydride (Towle *et al*., 1968, Erskine, 1970)

Product	Synthesized from	Production* Quantities (10^6 lbs.)	Use
Anthraquinone dyes	PAN and benzene or other aromatic hydrocarbons (Friedel-Crafts reaction)	51.97	Dye
Phthalocyanine		1.76	Dye
Xanthene		1.11	Dye
2-chloroanthraquinone	PAN and chlorobenzene	0.53	Dye intermediate
Quinizarin (1,4-dihydroxy-anthraquinone)	PAN and p-chlorophenol	1.61	Dye intermediate
Rhodine dyes	PAN and aminophenols		One of the xanthene dyes
Fluorescein	PAN and resorcinol		One of the xanthene dyes
Anthraquinone	PAN and benzene		Dye intermediate
Phthalimide	PAN and ammonia		Phthalocyanine dye intermediate (general intermediate for other chemicals)

TABLE V

(continued)

Product	Synthesized from	Production* Quantities (10^6 lbs.)	Use
o-Phthalonitrile	PAN, ammonia, and then phosgene		Phthalocyanine dye intermediate (general intermediate for other chemicals)
Phenolphthalein	PAN and phenol		pH indicator and medicinal (laxative)
Methyl anthranilate	Derivative of phthalimide	.25 (sales)	Perfume
Tetrachloro- and tetrabromophthalic anhydride	PAN, bromine or chlorine in presence of sulfuric acid		Impart fire resistance to resins and foams
Sulfathalidine			Medicinal chemical
Lead salt of phthalic acid			Stabilizer for PVC
Diallyl phthalate	PAN and allyl alcohol	> 5.0 (Erskine, 1970)	Cross-linking agent in unsaturated polyesters
Benzoic acid (only in Europe)	PAN decarboxylation		Intermediate
Terephthalic acid (only in Japan)	Phthalic acid salt thermal rearrangement		Intermediate
Sodium salt of phthalic acid	PAN and sodium hydroxide	small amount	Tanning industry

*U.S. Tarriff Commission, Synthetic Organic Chemicals, U.S. Production and Sales, 1970.

B. Isophthalic Acid

The largest application of isophthalic acid is in the production of unsaturated polyester resins, as can be seen in Table VI.

TABLE VI

Consumption of Isophthalic Acid
(Blackford, 1970) (10^6 lbs.)

	Isophthalic Polyester Resins	Alkyd Resins	Exports	Miscellaneous	Total
1965	30	20	10	10	70
1966	30	20	15	10	75
1967	35	20	20	10	85
1968	35	25	25	10	95
1969	40	25	15	15	95

These isophthalic polyesters cost more than the general-purpose polyesters (mostly PAN based) but have been able to capture some of the market because they have better chemical resistance, more strength, and better high temperature properties. The largest use of the isophthalic polyesters is in glass-fiber-reinforced plastics which are utilized in bodies of cars (e.g., Corvette sports car body), trucks, trailers, and boats, and in corrosion resistant equipment and pipe. The molded plastic applications include serving trays, surfboards, bowling balls, skateboards, archery equipment, fishing rods, safety helmets, highway lane markers (dots), gel coats, and heat and detergent-resistant buttons (Blackford, 1970).

Isophthalic acid has also entered another market of phthalic anhydride-saturated polyester (alkyd) resins. Their initial use was in consumer paints and enamels, but the field of industrial coatings is exhibiting a faster growth rate. Isophthalic acid has replaced PAN in many specialty coatings markets because it imparts increased film strength, higher gloss, faster drying, and higher melting properties to the resins.

Miscellaneous applications include use in the preparation of dioctyl isophthate plasticizers (~2 x 10^6 lbs./yr.) and use as modifiers and cross-linking agents in polyester fibers and films, polyamide fibers, and high-temperature-resistant polymers (e.g., polybenzimidazoles). Small amounts of the isophthaloyl chloride find use in dyes, resins, films, and protective coatings (Blackford, 1970).

C. Terephthalic Acid (TA) and Dimethyl Terephthalate (DMT)

Nearly all (~80-90%, Frey, 1970) the TA and DMT manufactured is used to produce polyethylene terephthalate, the polymer used for making fibers and films. The quantity of TA-DMT used for fibers (1,494 x 10^6 lbs.) far exceeds the quantity used for film (121 x 10^6 lbs.) in 1969 (Frey, 1970). Polyester fibers are mostly used in textile products, although a considerable amount of filament yarn is used as tire cord. The film is used for magnetic tapes, electrical insulation, packaging, and photographic applications.

Small amounts (~10 x 10^6 lbs.) are used in the preparation of adhesives, herbicides, printing inks, and specialty coatings and paints (Frey, 1970). Terephthalic acid has also been used as an animal feed supplement to increase the levels of antibiotics in the blood serum and liver (Towle *et al.*, 1968).

D. Trimellitic Acid (TMA) and Trimellitic Anhydride (TMAN)

Trimellitic anhydride, the commercially used form, finds applications in plasticizers, alkyd resins, unsaturated polyesters, printing inks, resin intermediates, adhesives, molding resins, and dyes. The largest outlet for TMAN is in the preparation of specialty plasticizers such as the triisooctyl and triisooctyl esters of trimellitic acid. These plasticizers find use with vinyl resins where permanency is required, as in polyvinyl chloride wire insulation, upholstery, refrigerator gasketing, and thin fabric coatings. Other major applications include use in the production of poly (amide-imide) polymers for use in wire enamels and electric-insulating varnishes, poly (ester-imide) formulations for wire enamels, and water-based alkyd finishes in the coatings industry.

E. Trimesic Acid (TMSA)

Trimesic acid is still in the development stage in terms of commercial use. It is used in small quantities as a crosslinking agent and the acid esters are used as plasticizers (Towle, et al., 1968).

F. Pyromellitic Acid (PMA) and Pyromellitic Dianhydride (PMDA)

The dianhydride of pyromellitic acid is the commonest commercial form. PMDA when combined with aromatic diamines gives excellent high-temperature-resistant polyimide polymers, which find use in molded parts, film, fibers, and insulating varnishes. The dianhydride is also used as a crosslinking agent for epoxy and other resins (Towle, et al., 1968).

IV. Current Practices

A. Phthalic Anhydride

Phthalic anhydride is sold and transported in both the solid and molten form. In the solid form it is usually sold in flakes packaged in 80 lb. multiwall paper bags. Small amounts of phthalic anhydride are sold in one-trip containers holding up to about 2,000 lbs. A red label is not required. Fairly sizable quantities of phthalic anhydride are shipped in the molten form to large users by tank cars or trucks. The molten PAN will burn if ignited and its vapor may form an explosive mixture with air. The Manufacturing Chemists Association (1956) recommends that container bags be incinerated and that the PAN wastes be disposed of by dumping in a special area isolated from all operations and where no contamination of a drinking water supply will be involved.

B. Isophthalic Acid

Isophthalic acid ismost commonly shipped as a free-flowing powder in 50 lb. multiwall paper bags. For large users, one trip palletized fiberboard containers of 2,000-lb. capacity or hopper-cars may be used. A red label is not required.

C. Terephthalic Acid and Dimethyl Terephthalate

Neither TA or DMT require a red label. The technical-grade TA is generally supplied in 50-lb. multiwall paper bags or 55 gallon fiber drums while the polymer-grade acid is shipped in 55 gallon fiberboard containers (225-325 lb. net), palletized fiberboard cartons (1200-1400 lb. net), returnable containers (approximately 4,000 lb. net) and hopper cars. DMT is usually formed into almond-shaped briquettes, weighing about 5 g each, and shipped in returnable 98- or 100-ft.^{3} metal containers handling 4600-5200 lb. or in smaller shipments in bags or 55 gallon fiberboard drums.

D. Trimellitic Anhydride

Trimellitic anhydride is shipped as a solid either in flake or powder form. The flakes and powders are shipped in 50 lb. multiwall paper bags and fiber drums, respectively, and neither requires a red label.

E. Pyromellitic Dianhydride

PMDA is usually shipped as a white powder in polyethylene bags in fiber drums. The compound is sensitive to moisture and will hydrolyze to the acid when exposed to atmospheric moisture for appreciable lengths of time.

V. Environmental Contamination

Although phthalate esters are often cited as widespread environmental contaminants (Mayer et al., 1972; Shea, 1972; Hites and Biemann, 1972; Fishbein and Albro, 1972) from their use as plasticizers, little is known about the extent of environmental contamination from benzenepolycarboxylic acids, anhydrides and salts. No background level monitoring data is available. However, these compounds are used in large quantities (phthalic anhydride ~800 x 10^6 lbs.; TA-DMT ~3,300 x 10^6 lbs.) and have often been cited as pollutants on a local basis.

Phthalic anhydride is most often noted as an air pollutant because of its low eye irritation threshold (4 ppm by volume). The manufacturing plants are notorious for odor control problems (Turk et al., 1972; Spitz, 1968). The major source is the process off-gas consisting of large volumes of air contaminated with small quantities of organic vapor (see Table VII) (Fawcett, 1970).

TABLE VII

Contaminants in Phthalic Anhydride Process Off-Gas
(Fawcett, 1970)

Contaminant	Concentration Ranges (ppm by vol)
Phthalic Anhydride	40-200
Maleic Anhydride	100-600
Naphthoquinone	10-30
Benzoic Acid	5-40
Aldehydes as CH_2O	10-100
Carbon Monoxide	1000-10,000
Carbon Dioxide	6000-50,000

Scrubbing is capable of removing in excess of 99% of all the organic acids, but requires neutralization prior to sewering or discharge to a watershed. The most common form of control is catalytic oxidation equipment. This type of control or direct flame incineration are estimated to produce at least 90% combustion of organic contaminants. Without such controls, a 100 million lbs. phthalic anhydride plant would discharge from less than 300 to over 1200 lbs./hr. of organics. Other minor air emissions points from phthalic anhydride plants include spills and losses from tank car or truck loadings, process venting during refining, and emissions from flaking and bagging (Fawcett, 1970). Water pollution problems from phthalic anhydride plants are likely to be small since most processes are dry. When wet scrubbing is used to control air pollution, the water may sometimes be disposed of in a water shed, but in most cases is sent to a sewage treatment plant. Phthalic acid wastes have been noted in waste waters from paint and varnish industries (Mirkind and Sporykhina, 1968) and alkyd resin plants (Minkovich, 1960).

Evaluation of environmental contamination from production, use or disposal of the other benzenepolycarboxylates has not been reported.

VI. Monitoring and Analysis

Few analysis methods, which might be used to monitor environmental samples containing extremely low concentration of the chemicals, have been reported for benzenepolycarboxylates. Most of the methods reported were used to detect the benzenepolycarboxylate in air or waste water effluents from industrial concerns. For example, Yurko and Volkova (1964) used a colorimetric method (react sodium salt of the acid with sulfuric acid and resorcinol) to determine phthalic anhydride in waste water (limits of detection not reported). Slavgorodskii (1965) reported an ethanol absorption with spectrophotometric quantification method for determining phthalic anhydride in atmospheric samples (no limits of detection). Kogar (1958) also determined phthalic anhydride in air, but used a filter paper collection system with polarographic quantification (again no limits of detection reported). A photometric technique for μg amounts of phthalic acid, and the anhydride, ester, imide, and substituted monoamide derivatives in both air and water samples was used by Ciuhandu et al. (1969). Air samples were collected in alcohol. Quantification was determined by heating the sample to 210°C with 83% $ZnCl_2$, cooling the sample, adding Na_2SO_3 and then 25% NH_3, filtering, and measuring the absorbance at 488 nm. The relative error was less than 3% for 10 μg of phthalic anhydride. Levchenko et al. (1968) used gas-chromatographic analysis to detect benzenepolycarboxylic acids from a terephthalic acid plant (toluene oxidation process). The acids were first esterified with diazomethane to the methyl esters. Fishbein and Albro (1972) have also used methylation and gas-chromatography for structure assignment of the acid moiety of the ester found in bovine heart muscle mitochondria.

Two relatively sensitive and specific analysis techniques have been reported for phthalic and terephthalic acids. Kumamaru (1968) reported an atomic absorption technique for determining phthalic acid by solvent extraction with neocuproine-copper(I) chelate. Reproducibility of the method was established at a concentration of $4.00 \times 10^{-5}M$ in phthalic acid (approximately 6 ppm). The method is rapid and accurate and free from isomeric interferences (isophthalic, terephthalic and benzoic acids). Giang *et al*. (1967) used a fluorometric method with the amino derivative of terephthalic acid for determining residues in chicken tissues. The method was reported to be sensitive to 0.1 ppm.

VII. Chemical Reactivity (Towle et al., 1968)

The chemical reactivity of benzenepolycarboxylates is characteristic of the two major organic functionalities - the benzene moiety and the carboxylate moiety. The benzene moiety will undergo typical aromatic substitution and addition reactions such as halogenation, nitration, sulfonation and hydrogenation. The rate and ease of reaction is dependent upon the number and isomer distribution of the carboxylate moiety.

The major commercial uses of the benzenepolycarboxylates are dependent upon the reactivity of the carboxylates. Esterification is the most important. Reaction of the acid or anhydride with monofunctional alcohols either at elevated temperatures or at low-moderate temperatures with strong acid catalyst yields esters which are used for plasticizers. Reactions with polyfunctional alcohols yield polyester polymers which provide plastics, fiber and film by-products. Even dimethyl terephthalate undergoes transesterification with simple alcohols, diols, triols, and other polyglycols in the presence of a basic catalyst.

Acid compounds which contain ortho-substituted dicarboxylates (PA, TMA, and PMA) will form anhydrides at elevated temperatures or under anhydrous conditions. When the anhydride form is possible, it is the normal commercial product. An equilibrium exists between the acid and the anhydride as depicted in Figure 1.

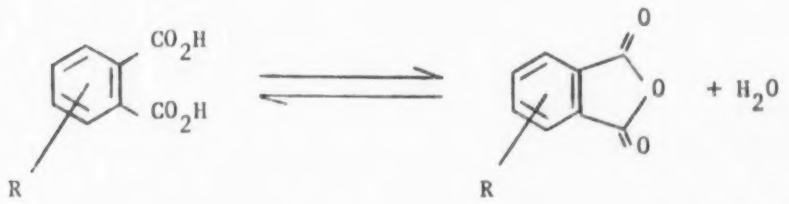


FIGURE 1
Equilibrium Between Benzenecarboxylic Acids and Anhydrides

Therefore, any anhydride that is released into the environment (water abundant in most cases) is likely to have some of it converted into the acid form.

Acid halides may be formed by the reaction of the acid with thionyl halide or phosphorus pentahalide. The benzenecarboxylates will react with ammonia to form salts, amides, and imides. Metal salts can also be formed from the acid and they are somethimes used to purify the acid for use in polyesters. The equilibrium between the acid and its anion conjugates is pH dependent in aqueous solution (Figure 2) and, therefore, the solubility in an aqueous solution is pH dependent. The benzenecarboxylate compounds also undergo Friedel-Crafts condensations with

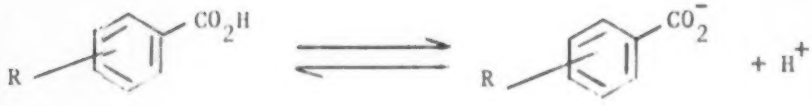


FIGURE 2

Equilibrium between Benzenecarboxylic
Acid and Its Anion Conjugate

other aromatic systems to yield ketones and quinones (e.g., phthalic anhydride ——————→ anthraquinone).

Thermal and oxidative stability of the benzenepolycarboxylate compounds is not very high. They will burn and some will explode when combined with air at elevated temperatures. Incineration is used as a pollution control technique.

VIII. Biology

The biology of most benzenepolycarboxylic acids has not been extensively studied. Terephthalic acid, however, is an exception, perhaps because of its use as an additive in poultry feed in order to retard the excretion of antibiotics (Boyd et al., 1960).

A. Absorption

When injected intraperitoneally into rabbits, terephthalic acid is rapidly absorbed by the plasma reaching a maximum plasma level within one hour. In oral administration, the maximum plasma level is not reached for 8-10 hours with an administration of 200 mg/kg resulting in a plasma concentration of 11.7 μg/ml. Thus, in oral administration, the limiting factor on plasma concentration is gastrointestinal permeability (Hoshi et al., 1966). Terephthalic acid is readily absorbed by the gastrointestinal tract with 70% or more of an oral dose probably being absorbed unchanged by the stomach and small intestine within 4-24 hours and 22% absorbed by the cecum and large intestine (Hoshi and Kuretani, 1967). In that there is some evidence that both terephthalic and phthalic acids can cause internal damage on inhalation (Sanina, 1965; Stepanov et al., 1962), similar absorption across alveolar membranes might be supposed but no such absorption has been documented.

B. Excretion

After ingestion, terephthalic acid is rapidly excreted from the body. Biological half lives for terephthalic acid in rabbits and rats have been found to be 1.8 hours and 1.2-3.3 hours, respectively (Hoshi _et_ _al_., 1966; Hoshi and Kuretani, 1967). Using radioactive terephthalic acid (carboxy-^{14}C), it was found that almost all of the compound is excreted in the urine after a 24-hour period with small amounts appearing in the feces (see Table VIII).

TABLE VIII

Excretion of Terephthalic Acid after the Oral Administration of a Single Dose of 85 mg./kg. to Rats [Hoshi and Kuretani, 1967]

Time (hr.)	Excreted TPA (%)[a)] Urine	Feces	Total
0 ∿ 2	10.8 ± 8.5	--[b)]	10.8 ± 8.5
0 ∿ 4	33.6 ± 7.1	--[b)]	33.6 ± 7.1
0 ∿ 6	61.5 ± 7.8	--[b)]	61.5 ± 7.8
0 ∿ 8	82.1 ± 7.5	0	82.1 ± 7.5
0 ∿ 24	93.5 ± 7.6	3.3 ± 2.1	96.8 ± 6.4
0 ∿ 48	93.8 ± 7.6	3.3 ± 2.1	97.1 ± 6.4

a) Mean value ± S.D. (5 rats). b) No evacuation.

C. Transport

Terephthalic acid is readily transported throughout the body (see Distribution) by the blood and eliminated in the urine via the kidneys as indicated in the preceding section.

D. Distribution

As can be seen in Table IX, terephthalic acid is distributed throughout the body a very short time after ingestion.

TABLE IX

Distribution of Terephthalic Acid After a Single Oral Dose of 85 mg/kg [Hoshi and Kuratani, 1967]

Time (hr)	TPA contents (μg/g or ml) a)					
	2	4	6	8	24	48
Plasma	10.38± 1.74	6.75±2.05	2.96±0.32	2.38±0.37	0	0
Kidney	58.52±10.71	25.71±4.60	15.74±3.03	8.54±1.67	0.41±0.04	0
Liver	31.25± 2.88	12.96±2.18	8.14±1.40	5.13±0.56	0.13±0.04	0
Brain	0.98± 0.05	1.22±0.07	1.17±0.11	1.32±0.08	0.07±0.01	0
Skin	6.04± 1.33	2.91±0.45	2.14±0.42	1.90±0.29	0.06±0.04	0
Lung	4.19± 0.34	1.72±0.40	1.34±0.04	0.63±0.13	0	0
Pancreas	3.11± 0.37	1.06±0.09	0.63±0.16	0.38±0.05	0	0
Spleen	1.30± 0.16	0.47±0.09	0.34±0.11	0.22±0.04	0	0
Adipose tissue (white)	0.87± 0.22	0.45±0.05	0.36±0.09	0.16±0.02	0	0
Heart	2.53± 0.41	0.84±0.19	0.61±0.19	0.29±0.05	0	0
Muscle (thigh)	0.72± 0.11	0.31±0.05	0.24±0.10	0.09±0.01	0	0
Bone (femur)	0.41± 0.14	0.12±0.04	0.10±0.04	0	0	0
Blood cell b)	0.43± 0.07	0.32±0.13	0.18±0.06	0	0	0
Uterus	5.67± 1.31	2.15±0.68	1.70±0.54	0.70±0.17	0	0
Ovary	4.4 ± 0.8	1.5 ±0.1	1.1 ±0.4	0.7 ±0.2	0	0
Salivary gland	3.16± 0.68	1.58±0.33	1.00±0.08	0.81±0.22	0	0
Thyroid gland	3.0 ± 0.3	2.0 ±0.3	1.4 ±0.3	1.0 ±0.4	0	0
Pituitary gland	3.1 ± 0.4	2.2 ±0.6	1.1 ±0.3	0.9 ±0.1	0	0
Adrenal gland	2.1 ± 0.2	0.9 ±0.2	0.5 ±0.1	0.2 ±0.1	0	0

a) Mean value ± SE of each 5 rats b) Corresponding to 1 ml of whole blood

The relative amounts in the various tissues do not vary significantly with elimination and it is not accumulated in any tissues.

E. Metabolism

Although certain benzenepolycarboxylates may be metabolized by some microorganisms (see Metabolic Effects), there is no evidence of such metabolism in the higher animals. It has been demonstrated that terephthalic acid is not metabolized in the rat (Hoshi and Kuretani, 1967).

F. Metabolic Effects

The metabolic effects of benzenepolycarboxylic acids cannot be clearly related to their toxicity. As indicated in Table X, several of these compounds have been tested and found to competitively inhibit *cis*-Aconitase.

TABLE X

Inhibition of *cis*-Aconitase by
Various Benzenepolycarboxylic Acids at 10 mM
[Gawron & Birckbichler, 1971]

Acid	% Inhibition
Terephthalic	0
Isophthalic	3
Phthalic	5
Trimesic	20
Trimellitic	33
Pyromellitic	51

Hemimellitic acid has a similar inhibitory effect on citrate transport in rat liver mitochondria with an ED_{100} at 25 mM (Robinson *et al.*, 1971).

Terephthalic acid depresses the rate of dye excretion by the kidney at 300 mg/kg in rats (Yanai *et al.*, 1967) and has a similar effect on the rate of antibiotic excretion in chickens (Giang *et al.*, 1967).

IX. Environmental Transport and Fate

A. Persistence and/or Degradation

With the exception of benzenedicarboxylic acids, very little information is known about the environmental stability of the benzenepolycarboxylates. No reports of environmental monitoring for these compounds have been uncovered. No information on the chemical or photochemical stability under environmental conditions has been reported for any of the compounds. However, the biodegradibility of the disubstituted compounds has been studied by a number of researchers. Ribbons and Evans (1960) and Perry and Scheld (1968) were able to isolate microbes that were capable of using phthalic acid for a carbon and energy source. Ribbons and Evans (1960) isolated their microbes from an industrial phthalic acid waste treatment plant as well as from garden soil, manure, and coniferous litter. These authors were able to isolate 4,5-dihydroxyphthalate from the metabolism of phthalic acid and suggested the following metabolic pathway.

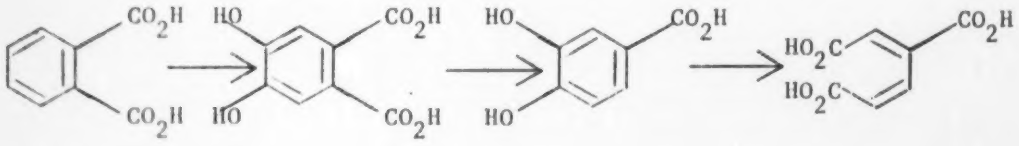


FIGURE 3.
Metabolism of Phthalic Acid
[Ribbons and Evans, 1960]

Saeger and Tucker (1973) studied the biodegradibility of phthalic acid with a river die away test (Mississippi River water). The results are tabulated in Table XI. It is difficult to assess the results since the phthalic acid degradation half-life is in between the time for a very degradable compound (LAS) and the time for a widespread environmental contaminant (DEHP).

TABLE XI

Biodegradibility of Several Phthalates
and Other Organic Compounds
Using a River Die-Away Test
[Saegar and Tucker, 1973]

Compound Tested	Initial Concentration (ppm)	Time for 50% Degradation (weeks)
1-Phenyl Dodecane-p-Sulfonate sodium salt (LAS)	3.2	0.8
Phthalic Acid	12.5	1.5
Butylphthalylbutyl Glycolate	1.0	0.2
Butylbenzyl Phthalate	1.0	0.2
Di-(2-ethylhexyl) Phthalate (DEHP)	1.0	2.5
Di-(heptyl-undecyl) Phthalate	1.0	3.0
Diundecyl Phthalate	1.0	2.5

Alexander and Lustigman (1966) studied the rate of microbial degradation of mono- and disubstituted benzenes. Although the method used had some shortcomings, a marked favorable effect of carboxyl groups on microbial decomposition was noted. Only benzoic acid and the isomeric phthalic acids were examined and, therefore, the environmental stability of the higher benzenepolycarboxylates is difficult to estimate. It is interesting to note that all the disubstituted benzenecarboxylic acids were slightly more stable than benzoic acid. If that trend is real, the higher substituted benzenecarboxylates should be more persistent.

B. Environmental Transport

No information on environmental transport of benzenepolycarboxylates was available in the surveyed literature.

C. Bioaccumulation

Metcalf _et al_. (1973) have studied the uptake of di-2-ethylhexyl phthalate (DEHP) in aquatic organisms utilizing a model ecosystem and both phthalic acid and anhydride have been isolated as metabolites. However, the levels detected were, for the most part, due to uptake of DEHP and degradation in the organism to the acid or anhydride.

X. Toxicity

A. Human Toxicity

Of the benzenepolycarboxylic compounds examined, only phthalic acid and its anhydride have aroused much interest as human toxicants, with the concern focusing almost exclusively on potential occupational hazards. Both compounds are generally considered to have low but significant levels of human toxicity by any of three routes: eye contact, skin contact or inhalation. A fourth possible route, ingestion, has not been reported for humans (Amer. Indust. Hyg. Assoc., 1967).

Eye Contact: Phthalic anhydride has been reported to effect the adaptability of the human eye at 920 mg/ℓ but not at 550 mg/ℓ (Slavgorodskii, 1967). At higher concentrations, PAN may cause inflamation of conjunctiva similar to its effect on other mucous membranes being largely due to the hydrolysis of PAN to PA (Amer. Ind. Hyg. Assoc., 1967).

Skin Contact: Similar to ocular damage, skin irritation seems to be caused primarily by PA rather than PAN. Dry skin does not respond immediately to PAN, but if the skin is not thoroughly cleansed, inflammation will result. In the more severe exposures, sores may develope with subsequent shedding and flaking (Manufact. Chem. Assoc., 1956). However, with prompt treatment, even massive exposure does not result in a severe response (Manufact. Chem. Assoc., 1966). Although PAN is reported to cause sensitization in some individuals over long periods of exposure (Amer. Indust. Hyg. Assoc., 1967), detailed descriptions of this syndrome have not been encountered. In an outbreak of acute dematitis associated with PAN production, naphthaquinone was eventually identified as the probable toxic agent (Kito et al., 1953), but to what extent presumed PAN dermatitis may be due to product contaminants has not been determined.

Inhalation: Exposure by inhalation may proceed in much the way as skin or eye contact. The mucous membranes and the upper respiratory tract are the primary sites of attack allowing ready hydrolysis of PAN to PA (Manufact. Chem. Assoc., 1956). In some cases, prolonged occupational exposure leads to severe inflammation of the upper respiratory tract that may result in bronchitis as well as severe nasal and dermal irritation (Anon., 1957). PAN has also been associated with an increase in vascular penetrability causing a net loss of proteins (Vychub, 1965) similar to the effect noted in rabbits (Tsyrkunov, 1966). Along with a decrease in proteins, PAN also causes an exposure dependent decrease in Vitamin C levels in the blood (Vychub and Vychub, 1965). While such changes do not seem severe enough to cause manifest pathologic conditions, Markman and Savinkina (1964) have reported progressive damage to the respiratory apparatus with occupational exposure to PAN. Upon X-ray, exposures of two years showed a more pronounced outlining of the pulmonary vascular system. Workers with a three year exposure showed an increase in fibrous tissue and distention of the pulmonary vessels. Those exposed for six years evidenced marked fibrosis of the lungs. In a similar study, Khasis (1964) concluded that occupational exposure to PAN may result in subclinical respiratory insufficiency.

B. Toxicity to Birds and Non-human Mammals

1. Acute and Subacute Toxicity

a. Phthalic Anhydride

Although oral toxicity has not been a problem in occupational exposure, the acute oral toxicity has been determined in some laboratory animals. At concentrations of 0.68g/kg body weight no toxic response is observed in rats (Pludro _et al_., 1969). The LD_{50} for mice has been measured as 2.21g/kg. body weight. Yet unlike the damage caused through the more common routes, ingestion does not effect the skin, eyes, or upper respiratory tract (Zhilova and Kasparov, 1968). However, ocular, dermal, and respiratory exposure do elicit responses comparable to those of man. Direct application to the eyes of rabbits causes conjunctivitis (Zhilova et al., 1966). Dermal application of 200 g/ℓ ethanol at 0.5 - 1 ml/day to rabbit skin causes acute inflammation and changes in blood vessel permeability (Tsyrkunov, 1966). However, direct application to the isolated frog heart will cause beat failure at 1 g/ℓ

(Stepanov, 1964). Acute inhalation toxicity data is not available but 350-400 g/ℓ has been shown to increase the amino nitrogen level in rat urine (Zhilova and Kasparov, 1966).

b. Phthalic, Isophthalic and Terephthalic Acids

In studying the comparative toxicity of these compounds through the intraperitoneal injection of mice, Caujolle and Meynier (1958) determined the following order of toxicity: PA > TA > IA [see Table XII].

TABLE XII

Toxicity of Benzenedicarboxylic Acids to Mice 24 Hours After Intraperitoneal Injection [Caujolle and Meynier, 1958]

	LD_{50}	LD_{100}
Phthalic Acid	1.67 g/kg	2.41 g/kg
Terephthalic Acid	3.70 g/kg	4.50 g/kg
Isophthalic Acid	4.20 g/kg	5.60 g/kg

Of these, however, only terephthalic acid and its disodium and dimethyl derivatives have received appreciable toxologic evaluation. Other studies indicate considerably lower lethal doses for terphthalic acid than those given by Caujolle and Meynier (1958) [see Table XIII].

TABLE XIII

Lethal Doses for Terephthalic Acid by Intraperitoneal Injection of Mice

Mice	LD_{50}	LD_{100}	Duration	Source
≈ 25 g *	1.43 g/kg	-----	3 days	Hoshi et al., 1968
≈ 20 g #	1.9 g/kg	3.2 g/kg	1 day	Grigas et al., 1971
≈ 20 g *#	3.7 g/kg	4.5 g/kg	1 day	Caujolle and Meynier, 1958

* = female # = male

Obviously, any number of parameters could account for such discrepancies. The comparison, however, does indicate the difficulty in precisely determining lethal doses even within a single genus. Also, the difference between lethal and physiologically significant doses deserves emphasis in dealing with a compound that may not readily cause death but which may cause significant alterations in body function. Hoshi and coworkers (1968), while noting an LD_{50} of 1.43 g/kg intraperitoneally, found that 300 mg/kg will cause renal function depression. Intraperitoneal injection of rats gave a similar LD_{100} to that determined by Grigas and associates (1971) for mice. Rats intraperitoneally injected with 3.5 g/kg showed depressed neural and liver functions, a decrease in plasma Vitamin C, and an increase in the globulin fractions of serum (Slyusar and Cherkasov, 1964). As would be expected, intravenous injection seems to cause a lethal response at lower concentrations. Dogs are fatally intoxicated with

767 mg/kg given intravenously at the rate of 2 mg/kg/min, with death immediately preceded by respiratory arrest (Grigas et al., 1971). Thus, this form of acute poisoning may be physiologically unrelated to death by other routes.

Orally, terephthalic acid is considerably less toxic than injected doses. In ad libitum feeding of .5% terephthalic acid in feed over a seven day period, the LD_{50} is calculated to be over 5 g/kg body weight (Hoshi et al., 1968). In single induced dose feeding experiments, 10 g/kg body weight gave an LD_{40} in 6-12 days after exposure, with death characterized by cellular infiltration of the mucous membrane of the gastrointestinal tract, and fluid accumulation and congestion of the internal organs. Lower doses, while not fatal, produced marked physiological changes. At 5 g/kg body weight, both respiratory depression and pronounced vascular disorders were noted over a 24 hour period. Even at 0.5 g/kg, a brief period of stimulated activity and subsequent depression was elicited (Savina, 1965).

Lethal data are not available for the inhalation of terephthalic acid, but skin irritation and respiratory stimulation results in rats after exposure to .002-.005 mg/ℓ for 2 hr/day after 5 days. More prolonged exposure leads to skin erosion and unspecified vascular, respiratory, and neural changes (Sanina, 1965).

Both dimethylterephthalate and disodium terephthalate cause the same type of toxic response as terephthalic acid (Hoshi _et_ _al_., 1968; Slyusar and Cherkasov, 1964). Bearing in mind the limited reliability of comparative toxicity data, the degree of potency of the various terephthalates - based on the data from Table XIV - may be arranged as follows: terephthalic acid > dimethylterephthalate > disodium terephthalate.

TABLE XIV

Acute Toxicity of Terephthalic Compounds
in Mice and other Mammals

LD_{50} (mg/kg)

Route	Terephthalic Acid	Disodium Terephthalate	Dimethyl-terephthalate
Oral	> 5000*	6300 (5000)*	‡ > 3200***
	‡ 3500**** (LD_{100})		‡ 4500**** (LD_{100})
Subcutaneous	---	8600 (6800)*	---
Intraperitoneal	1430*	4600 (3600)*	‡ > 3200***
Intravenous	+ 767**	≥ 1300 (≥1000)*	---

( ) calculated as free acid   + dog ‡ rat

* Hoshi _et_ _al_., 1968
** Grigas _et_ _al_., 1971
*** Fishbein and Albro, 1972
**** Slyusar and Cherkasov, 1964

c. Trimellitic Acid and Anhydride

The only higher benzenecarboxylic acid encountered in the literature was trimellitic acid and the corresponding anhydride. On oral administration to both rats and mice, TMA and TMAN elicit the same basic symptoms: swelling of the internal organs and skin, and respiratory depression (Batyrova and Uzhdavini, 1970).

TABLE XV

Acute Oral Toxicity (LD_{50}) of TMA and TMAN to Mice and Rats [Batyrova and Uzhdavini, 1970]

	TMA	TMAN
Mice	1.25 g/kg	2.50 g/kg
Rats	1.90 g/kg	6.25 g/kg

As with phthalic acid, inhalation of trimellitic acid seems to primarily attack the mucous membranes causing signs of respiratory distress.

2. Chronic Toxicity

Long term low level exposure studies have been encountered only for phthalic anhydride.

In induced oral administration to rabbits at 20 mg/kg body weight/day over a 120 day period, the number of leukocytes and blood aldolase activity increased (Zhilova and Kasparov, 1966). Over the same period, rats fed 100mg/rat/day showed considerable weight loss but no lethality. Besides irritation of the mucous membranes of the trachea, bronchi, and stomach, degeneration was noted in the liver, kidney, and myocardium (Reznik and Petrishina, 1963).

On inhalation, phthalic anhydride elicits a dosage dependant response in rats. A 45 day continuous exposure to 20 mg/l reduces the dehydroascorbic acid content in the testicles. At concentrations of 100 mg - 200 mg/l over a two week period, however, there is a reduction in dehydroascorbic, ascorbic, and neucleic acids in the testicles as well as a decrease in fecundity (Protsenko, 1970). Motor activity is influenced by continuous exposure to 540 mg/l for 70 days (Slavgorodskii, 1967). Only at the extremely high concentrations of 30-90 g/l is an approximate LD_{50} obtained for rats when exposed for two unspecified periods per day for 135 days. The pathologic signs are similar to those of oral administration except that the weight loss is slight and the eyes are severely irritated (Reznik and Petrishina, 1963). Rabbits may be considerably more sensitive than rats, showing abnormal hemoglobin and irritation to the eyes and respiratory tract at concentrations of 1 mg/l and exposures of 1-2 hrs/day over a 60-105 day period (Stepanov et al., 1962).

3. Sensitization

The ability of phthalic anhydride to cause sensitization to both humans and other mammals is widely accepted in the literature (Manufact. Chem. Assoc., 1956). However, detailed studies of this response have not been encountered. Dueva and Aldyreva (1969) attribute strong allergenic properties to the phthalic acid radical but the mechanism is not discussed.

4. Teratogenicity

As a metabolite of thalidomide, phthalic acid has been studied for teratogenic effects. Although PA was shown not to have a teratogenic effect in mice (Koehler et al., 1971), it does stimulate over a two-fold increase in chick embryo teratism (Verrat et al., 1969). Although this does not indicate a high degree of teratogenicity, the studies thus far conducted cannot be considered definitive.

5. Carcinogenicity

The benzenepolycarboxylic acids have not been implicated in carcinogenic agents in the studies thus far screened. Indeed, terephthalic acid may inhibit spontaneous mammary tumorigenesis and delay or prevent hepatic carcinogenesis by p-dimethylaminobenzene (Nagasawa and Fujinoto, 1973; Yanai et al., 1967).

6. Mutagenicity - no studies encountered.

7. Behavioral Effects - no studies encountered.

C. Toxicity to Lower Animals - no studies encountered.

D. Toxicity to Plants

The phytotoxicity of the benzenepolycarboxylates does not seem to have been extensively studied. In the only study thus far encountered, phthalic acid and unspecified derivatives of phthalic acid were not shown to have any effect on rice plants (Tomizawa and Koike, 1954).

E. Toxicity to Microorganisms

Phthalic acid is reported to have no toxic effects on 28 strains of Salmonella at concentrations of 25 mg/l and 200 mg/l (Vecchio *et al*., 1949). At concentrations of 1000 mg/l, however, it causes a twelve fold decrease in the growth of the flagellate protozoa *Ochromonas danica* (Frank *et al*., 1963). Also, several benzenepolycarboxylic acids were found to agglutinate cultures of *Escherichia coli* in the following order of potency: terephthalic acid > phthalic acid > trimesic acid > hemimellitic acid (Maccacaro and Dettori, 1960).

XI. Benzenepolycarboxylates: Summary and Conclusions

Of all the benzenepolycarboxylates, the terephthalates - DMT and TA - are by far the most widely used and represent a total annual production of over three billion pounds. Phthalic anhydride is the next in importance with an annual production approaching one billion pounds. Isophthalic acid is much less extensively used and is probably produced not much in excess of 100 million pounds yearly. Production figures for the more highly substituted benzenecarboxylic acids are not available. Although a meaningful quantitative estimate cannot be made by group, it seems likely that their total annual production is in excess of 15 million pounds, but does not exceed 50 million pounds. The trimellitic and pyromellitic compounds probably constitute the bulk of the higher benzenepolycarboxylate production.

Although these compounds are as a group produced in very large quantities, they are used mostly in the synthesis of other commercial compounds and thus large scale direct environmental contamination does not seem indicated. Almost all of the terephthalates and pyromellitics are bound as polymers. Similarly, most of the phthalates, isophthalates, and trimellitics are used in the formation of diesters for plasticizers, or polyesters for structural components. Consequently, the prime source of environmental contamination is likely to occur in manufacture and/or transport, where some degree of unintentional release must be expected. In view of the quantitites produced, even a small percentage of such loss could result in appreciable contamination. Further, the amount of benzenepolycarboxylate release from physical, chemical, or biological deterioration of the various end products may be significant. Many of these products are disposable and eventually subject to incineration or landfill.

Although certain benzenepolycarboxylate esters have received considerable attention as environmental pollutants, little is known about the actual degree or extent of acid or anhydride contamination, except for isolated reports of local pollution from manufacturing facilities. Along with this lack of monitoring information, the fate of benzenecarboxylates in the environment has not been conclusively demonstrated. Although more stable than benzoic acid, the disubstituted acids would seem to exhibit no exceptional degree of oxidative or thermal stability and are at least moderately biodegradable. If extrapolation from data on mono- and dicarboxylic acids is valid, the higher acids may prove quite stable but no supporting experimental evidence has been found. Information on bio-accumulation and environmental transport is also unavailable. Their physical properties do not necessarily preclude either atmospheric or aquatic transport but the relative importance of either mode will depend on the specific compound, the industrial process involved, and/or the method of commercial transport used. Bio-accumulation cannot be ruled out but does not seem indicated in the dicarboxylic compounds.

At realistic environmental concentrations, these compounds seem to have a low order of mammalian toxicity. For the disubstituted compounds, acute lethal toxicities are in the g/kg range in inverse order of production: PA > TA > DMT. Chronic pathology is only an order of magnitude lower (i.e., > 0.1 g/kg). However, the benzenedicarboxylates can elicit appreciable physiological changes in the 100 ppm range and minimal changes in the 10 ppm range. Even at low concentrations (1-4 ppm), phthalic acid will cause neurosensory excitation. Toxicity information on the higher substituted compounds is limited. The trimellitic compounds seem to have acute toxicities on the same order of magnitude (g/kg) as the dicarboxylic acids. Further evaluations of the toxic effects of these compounds have not been encountered. Based on enzyme inhibition studies, higher carboxylation might be expected to lead to increased toxicity but this supposition must remain questionable pending more conclusive experimental investigations. The non-mammalian toxicity of these compounds has received little attention. Possible pathogenesis to plants, invertebrates, and/or lower vertebrates cannot be discounted on the basis of the limited available information.

In interrelating data on the various factors involved, the benzenepolycarboxylates seem to present somewhat dichotomous potentials for environmental hazard. They are produced in immense quantity but are used primarily as chemical intermediates, thus limiting direct exposure to the environment. They have a very low order of mammalian toxicity but a correspondingly low threshold of irritability. However, because so little is actually known about the degree of contamination or possible environmental effects, a meaningful estimation of their potential environmental hazard is not possible at this time. Their uses and known biological effects would not seem to present any great threat. Yet, their extensive production and possible biological activity would seem to warrent a more careful resolution of the various problems outlined above.

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CHLOROPHENOLS

I. Physical Properties

All the chlorophenols, with the exception of o-chlorophenol, are solids at room temperature and all have a pungent, medicinal odor. They are generally insoluble in water, ethanol, ether and acetone, although the highly chlorinated phenols are soluble in ethanol, ether and acetone. The volatility of the compounds generally decreases and the melting and boiling point generally increase as the number of chlorine atoms substituted on the benzene ring increases. Table I presents some of the physical properties of the commercially important chlorophenols.

TABLE I

Physical Properties of Commercially Important Chlorophenols
(Doedens, 1964, Bevenue and Beckman, 1967)

Compound / Property	1-chloro-phenol	2-chloro-phenol	3-chloro-phenol	2,4-dichloro-phenol	2,6-dichloro-phenol	2,4,6-tri-chloro-phenol	2,4,5-tri-chloro-phenol	2,3,4,6-tetra-chloro-phenol	pentachloro-phenol	4-chloro-cresol	4-chloro-3,5-dimethyl phenol
Melting point (°C)	8.7	32.8	40-41	43-44	67	68	68	69-70	190	48-49	115-116
Boiling point (°C)	175-176	215-217	219	210-211	219-220	246	245-246	164/23mm	309-310	223	246
Dissociation constant (K_a) at 25°C	3.2×10^{-9}	1.4×10^{-9}	6.6×10^{-10}	2.1×10^{-8}	1.6×10^{-7}	3.8×10^{-8}	3.7×10^{-8}	4.2×10^{-6}	1.2×10^{-5}		
Solubility (g/100g)											
Water (25°C)	<0.1	0.26	2.71	slight		insol.		0.10	14-19 ppm		insol.
Ethanol (25°C)	>200	sol.	sol.	sol.		525 (methanol)		319 (methanol)	143		86
Ether (25°C)	>200	sol.	sol.	sol.	miscible						
Benzene (25°C)		sol.	sol.	sol.					158		
Chloroform (25°C)		sol.	sol.								6
Carbon Disulfide (25°C)		sol.	sol.								
Acetone						500		570	53		
Temperature at which the vapor pressure equals 1mmHg	12.1	44.2	49.8	53.0	59.5	76.5	72.0	100.0	.00011mm Hg (20°C)		

II. Production

Chlorophenols are produced by several companies in the U.S., but Monsanto and Dow are the most prominent. Table II lists the manufacturers and the products they produce. Plant capacities and locations for pentachlorophenol are also presented. As can be seen from Table II, Monsanto and Dow are the only companies that produce the lower chlorinated compounds. This relatively recent concentration of chlorophenol production has reduced the amount of information on production levels as is noted in Table III. The monochlorophenols have for many years been produced by only Monsanto and Dow and, thus, little information on production quantities is available. The _para_-substituted compound is used as a starting material for a number of by-products, but the only chemical which has reported production levels is 1,4-dihydroxylanthraquinone (quinizarin). However, large quantities of _p_-chlorophenol are used to synthesize 2,4-dichlorophenol. The percentage of the total _p_-chlorophenol production used in the other various products is unknown.

Production levels for 2,4-dichlorophenol are also unreported. However, productions figures for 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivatives are available, and since 2,4-D is the major outlet for the 2,4-dichlorophenol produced, approximate estimates of production can be derived. A similar relationship can be used for 2,4,5-trichlorophenol and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), although production levels for trichlorophenol were published up until 1968. Both 2,4-D and 2,4,5-T were produced in high quantities during the Vietnam War, but currently production levels are decreasing.

TABLE II

Chlorophenol Producers and Their Plant Locations and Capacities (Chemical Marketing Reporter, 1972; U.S. Tariff Commission, 1960-1971)

Producer	Capacity (Compound)* (10^6 lbs.)	Location	Compounds* Produced by the Company
Dover Chem.	-	Dover, Ohio	PCP
Dow Chemical Co.	15 (PCP)	Midland, Mich.	o-CP, p-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TCP, PCP, and others.
Hooker Chemical Corp.	-	Niagara Falls, N.Y.	2,4,5-TCP
Monsanto Co.	26 (PCP)	Sauget, Ill.	o-CP, p-CP, 2,4-DCP, PCP
Northeastern Pharmaceutical and Chemical Co.	-	Verona, Mo.	2,4,5-TCP
Reichhold Chem., Inc.	12 (PCP)	Tacoma, Wash.	PCP
Sonford Chem. Co.	18 (PCP) (not operating)	Port Neches, Tex.	PCP
Transvaal	-	Jackson, Ark.	2,4,5-TCP
Vulcan	7 (PCP)	Wichita, Kan.	PCP

*Compounds: o-chlorophenol (o-CP); p-chlorophenol (p-CP); 2,4-dichlorophenol (2,4-DCP); 2,6-dichlorophenol (2,6-DCP); 2,4,6-trichlorophenol (2,4,6-TCP); 2,4,5-trichlorophenol (2,4,5-TCP); 2,3,4,6-tetrachlorophenol (2,3,4,6-TCP); pentachlorophenol (PCP); 4-chlorocresol (4-CC); and 4-chloro-3,5-dimethylphenol (4-C-3,5-DMP).

TABLE III

Production of Chlorophenols and Related Products
1×10^6 lbs. (1×10^9 g)
(U.S. Tariff Commission 1960-1971; Doedens, 1964)

	p-chlorophenol (quinizarin production)	2,4-dichlorophenol (2,4-D + deriv.)	2,4,5-Trichlorophenol		2,3,4,5-Tetra-chlorophenol	Pentachloro-phenol
			2,4,5-T and derivatives	phenol and salts		
1960	1.12 (0.518)	70 (31.75)	14 (6.35)	10 (4.53)	9 (4.08)	39 (17.69)
1961	1.31 (0.594)	80 (36.29)	15 (6.80)	11 (4.99)	-	55 (24.95)
1962	1.43 (0.648)	80 (36.29)	19 (6.62)	12 (5.44)	-	39 (17.69)
1963	1.41 (0.640)	91 (41.26)	19 (8.62)	12 (5.44)	-	34 (15.42)
1964	--	108 (48.99)	24 (10.88)	14 (6.35)	-	37 (16.78)
1965	1.96 (0.889)	127 (57.61)	25 (11.34)	13 (5.90)	-	11 (4.99)
1966	2.35 (1.066)	141 (63.95)	33 (14.99)	18 (8.16)	-	43(19.50)
1967	2.07 (0.939)	161 (73.03)	42 (19.05)	25(11.34)	-	44(19.96)
1968	2.32 (1.052)	173 (78.47)	60 (27.22)	28 (12.70)	-	49(22.23)
1969	2.20 (0.998)	114 (51.71)	18 (8.16)	--	-	46(20.87)
1970	1.61 (0.730)	81 (36.74)	14 (6.35)	--	-	47(21.32)
1971p	1.71 (0.776)	53 (24.04)	--	--	-	51(23.13)

Of the chlorophenols, pentachlorophenol is produced in the largest quantity. It has maintained a steady growth over the past several years and is projected to continue at an annual growth rate of 4% (Chemical Marketing Reporter, 1972).

III. Uses (Doedens, 1964)

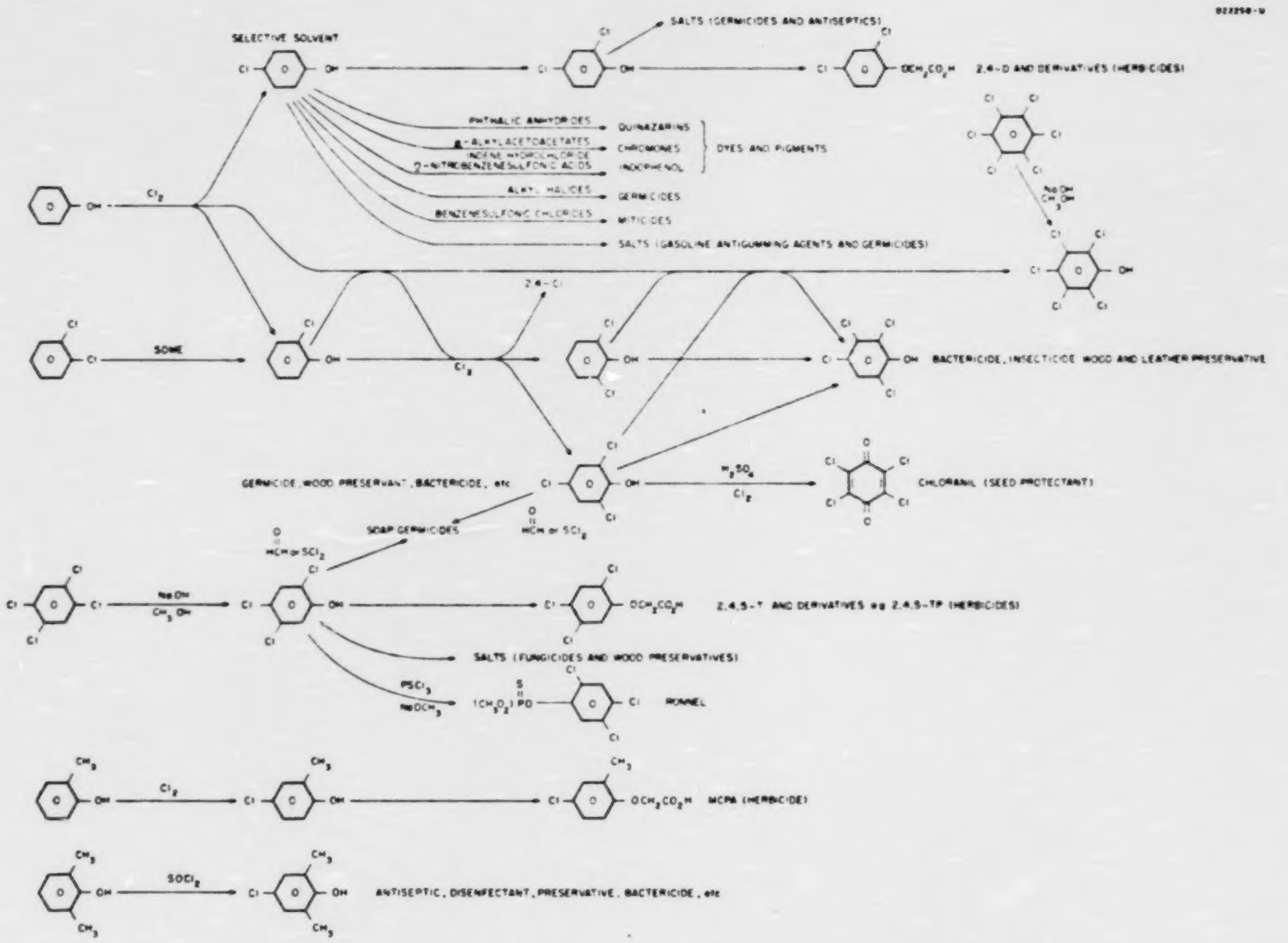
The chlorophenols have outstanding germicidal and insecticidal properties and enjoy numerous applications as flea repellents, fungicides, wood preservatives, mold inhibitors, antiseptics and disinfectants, etc. In general, the effectiveness in these applications increases with the degree of chlorine substitution. In addition, many chlorophenols are used as starting materials for the synthesis of compounds which find applications as dyes and pigments and pesticides. Figure 1 presents a flow diagram of the relationship between chlorophenol starting materials, intermediate compounds, and final products. The following will discuss each of the important commercial chlorophenol compounds.

A. *o*-Chlorophenol

In the United States, *o*-chlorophenol is produced as a by-product from the manufacture of *p*-chlorophenol by direct chlorination. Most of the production is used as a feedstock for chlorination to 2,4- and 2,6-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol, although some small quantities are sold.

B. *p*-Chlorophenol

The majority of *p*-chlorophenol produced is utilized as a starting material for the manufacture of other products. Large quantities of *p*-chlorophenol are used in the production of 2,4-dichlorophenol because of the high conversion to the 2,4-isomer. Other by-product



022250-V
SELECTIVE SOLVENT
SALTS (GERMICIDES AND ANTISEPTICS)
2,4-D AND DERIVATIVES (HERBICIDES)
PHTHALIC ANHYDRIDES
QUINAZARINS
β-ALKYLACETOACETATES
CHROMONES
INDENE HYDROCHLORIDE
2-NITROBENZENESULFONIC ACIDS
INDOPHENOL
DYES AND PIGMENTS
ALKYL HALIDES
GERMICIDES
BENZENESULFONIC CHLORIDES
MITICIDES
SALTS (GASOLINE ANTIGUMMING AGENTS AND GERMICIDES)
Cl2
SOME
2,4-Cl
BACTERICIDE, INSECTICIDE WOOD AND LEATHER PRESERVATIVE
NaOH
CH3OH
GERMICIDE, WOOD PRESERVANT, BACTERICIDE, etc
H2SO4
CHLORANIL (SEED PROTECTANT)
SOAP GERMICIDES
HCH or SCl2
2,4,5-T AND DERIVATIVES e.g 2,4,5-TP (HERBICIDES)
SALTS (FUNGICIDES AND WOOD PRESERVATIVES)
PSCl3
NaOCH3
(CH3O)2PO
RONNEL
MCPA (HERBICIDE)
SOCl2
ANTISEPTIC, DISENFECTANT, PRESERVATIVE, BACTERICIDE, etc

Figure 1.

Synthetic Routes to Chlorophenols and Chlorophenol By-Products (Doedens, 1964) compounds include quinizarins, chromones, indophenols, ether germicides, and sulfonic acid ester miticides. The salts find applications as antigumming agents for gasoline, wash liquids for fuel gas purification, and germicides. In addition, p-chlorophenol finds some use as a selective solvent in refining mineral oils and as a denaturant for ethanol.

C. 2,4-Dichlorophenol

The largest application of 2,4-dichlorophenol is as a raw material for the production of 2,4-dichlorophenoxyacetic acid (2,4-D) and derivatives. Alkali metal salts of the phenol have found utility as germicides, antiseptics, etc. 2,4-Dichlorophenol is also used in the synthesis of 2,2'-dihydroxy-3,5,3',5'-tetrachlorodiphenylmethane (mothproofing compound, antiseptic, and seed disinfectant), 2,4-dichlorophenyl benzenesulfonate (miticide), and other miscellaneous products.

D. 2,6-Dichlorophenol

The compound is usually produced as a by-product of further chlorination of o-chlorophenol. It is primarily used as feed stock for the manufacture of trichlorophenols, tetrachlorophenols, and pentachlorophenols.

E. 2,4,6-Trichlorophenol

2,4,6-Trichlorophenol has a variety of potential uses, but the quantities utilized is unknown. The compound has been cited as an effective germicide and has possible utility as a wood preservative, glue preservative, insecticide ingredient, bactericide, and antimildew treatment for textiles. It is used as a raw material in the production of the seed protectant, chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone). Reaction of 2,4,6-trichlorophenol with formaldehyde or SCl_2 yields compounds that are used as soap germicides.

F. 2,4,5-Trichlorophenol

The largest single use of 2,4,5-dichlorophenol is in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and related products [e.g., α -(2,4,5-trichlorophenoxyl)-propionic acid (2,4,5-TP)]. The compound is also used in the synthesis of Ronnel (2,4,5-trichloro-O,O-dimethylphosphorochlorodithioate and soap germicides (reaction with formaldehyde to form the bis-(methylene) derivative or with SCl_2 to form the thiobis derivative). The parent phenol compound is used as a fungicide by the adhesive industry for preserving polyvinylacetate emulsions; by the textile industry for preserving emulsions used in rayon spinning, rayon yarns, and silk yarns; and by the automotive industry for preserving rubber gaskets (Dow Chem. Co., 1969e). The sodium salt is used by the adhesive industry to preserve adhesives derived from casein as well as polyvinylacetate emulsion type adhesives and is added to leather dressings and finishes to prevent decomposition of nitrogenous components such as casein, gelatin, and egg albumen. The sodium salt is also added to metal cutting fluids and foundry core washes to prevent breakdown and spoilage and it is added to recirculating cooling water of cooling towers to control bacteria and fungi (Dow Chem. Co., 1969f).

G. 2,3,4,6-Tetrachlorophenol

The chief application of 2,3,4,6-tetrachlorophenol and its salts include uses as bactericides for latex preservation, insecticides, wood preservatives, and leather preservatives.

H. Pentachlorophenol

The major use of pentachlorophenol is as a wood preservative for poles, crossarms, and pilings (75% of total, Chemical Marketing Reporter, 1972). The sodium salt makes up 15% of the market (Chemical Marketing Reporter, 1972) and finds a number of antimicrobial uses in the leather, paper and fiberboard, photographic, paint, construction materials, and textile industries and has been used as a molluscicide. It is commonly used in 1 to 10% aqueous solutions. PCP has also been used in slime control in pulp and paper mills and as a fungicide and/or a bactericide in the processing of cellulosic products, starches, adhesives, proteins, leather, oils, paints, and rubber (Bevenue and Beckman, 1967).

I. 4-Chloro-o-cresol

The chief use of this compound is as a raw material for the manufacture of 2-methyl-4-chlorophenoxyacetic acid (MCPA) and its derivatives. MCPA is a plant-growth regulator, analogous to 2,4-D, which is widely used in Europe, but not widely applied in the United States probably because of different agricultural methods and climatic conditions.

J. Others

A variety of other chlorophenol antimicrobial agents are on the market. These include 4-chloro-3,5-dimethylphenol, 2-chloro-4-phenylphenol (Dowicide 4), 4-chloro-2-cyclopentylphenol (Dowicide 9), and a mixture of 4-chloro-2-phenylphenol and 6-chloro-2-phenylphenol (Dowicide 31 and 32).

IV. Current Practice

Chlorophenols are corrosive to the skin and eyes and some are readily absorbed through the skin in toxic amounts. Their vapors and dusts are very irritating and toxic. These adverse effects require that protective clothing and goggles be worn and a well ventilated area used during handling.

These compounds are transported by truck or rail. The pentachlorophenol (PCP) is packaged in 50 lb. multiwall paper bags, 300 lb. fiber drums, and 2500 lb. wire-bound boxes. Sometimes PCP is shipped in bulk trucks.

Information on disposal methods was not available.

V. Environmental Contamination

With the exception of pentachlorophenol, documentation of chlorophenol contamination of the environment is not very detailed. The lower chlorinated phenols have often been cited as being responsible for adverse taste and odor problems in water (Burttschell *et al*., 1959), but comprehensive monitoring data is not available.

One source of chlorophenol contamination which is often overlooked is the chlorine disinfection of phenol and cresol containing waste water effluents. Both Aly (1968) and Barnhart and Campbell (1972) have demonstrated that chlorination of phenols and cresols in aqueous solution can occur under conditions similar to those used for disinfection. With phenol, the reaction proceeded stepwise to provide the following compounds: *o*- and *p*-chlorophenol, 2,6- and 2,4-dichlorophenol and 2,4,6-trichlorophenol. Since chlorination of waste water effluents is a widespread practice for both industrial and municipal concerns, this source of chlorophenols may be quite significant.

Another source of environmental contamination is from the manufacture of chlorophenol by-products such as the herbicides 2,4-D, 2,4,5-T, and 2,4,5-TP and the many secondary products that use *p*-chlorophenol as a raw material. The extent of contamination from this source is dependent upon the number of formulation or manufacturing plants and the degree of waste treatment. Information on these parameters was not available in the reviewed literature, but several authors have determined the feasibility of treating wastes from the herbicide formulation plants (Mills, 1959; Sidwell, 1971) and the removal of 2,4-D derivatives from natural waters (Aly and Faust, 1965).

A third potential source of chlorophenol contamination of the environment is from the use of chlorophenol containing herbicides. The chlorophenol moiety of the herbicide has been shown to be a major metabolite in the environmental degradation of the herbicide (see Section IX A). Large quantities of herbicides (e.g., 2,4-D and 2,4,5-T) are used in the United States and, thus, provide a large potential source of chlorophenols in the environment.

As previously noted, the extent of contamination from the above sources is not well understood because of the limited monitoring information. However, Kawahara (1971) has reported the detection of 2,4-dichlorophenol in the Ohio River and a dam in West Virginia and a concentration of 6.6 ppb in a local Cincinnati water intake system was noted.

Contamination of the environment from pentachlorophenol appears to be widespread. Its use in sawmill products, wood chips (fungicide) and for slime control in pulp and paper mills make it highly suspectible to discharge into effluent receiving waters (Rudling, 1970). Rudling (1970) examined samples of water and fish in a lake that received effluents from a pulp mill and detected 3 μg PCP/ℓ in the water and 0.2 to 3.0 mg PCP/kg of fish tissue. Stark (1969) studied a lake where large fish kills were reported and found high concentrations of PCP. Cranmer and Freal (1970) have analyzed for PCP in human urine. They detected concentrations in the general population ranging from 2 to 5 ppb and even higher concentrations for individuals occupationally exposed to PCP. Similarly, an average of 5 ppb PCP in human adipous tissue from the general population was detected by Shafik (1973).

Buhler et al. (1973) examined the hourly fluctuations of PCP concentration in the enfluent from the Corvallis sewage treatment plant as well as the concentrations of PCP in the Willamette River. The average 24 hour concentration of PCP entering the treatment plant was 4.3 ppb, of which approximately 60% was removed during treatment. The highest concentration was during the middle of the day, reflecting a probable industrial discharge. The concentrations in the Willamette River (0.10 to 0.70 ppb) were at least tenfold higher than a calculated value derived from assuming the only source of PCP is municipal sewage. The authors suggest that industrial sources may explain the discrepancy. These authors also determined that water from a water treatment plant which used Willamette River water still contained 0.06 ppb PCP.

Recently contaminants found in chlorophenols have been cited as extremely toxic potential environmental pollutants (Rappe and Nilsson, 1972; Plimmer et al., 1973; Crossland and Shea, 1973; Elvidge, 1971; Jansen and Renberg, 1972). These contaminants, (chlorinated dibenzo-p-dioxins and dibenzofurans) are found in chlorophenols (trichlorophenol and PCP) which are synthesized from chlorobenzenes.

VI. Monitoring and Analysis

A variety of analytical techniques have been used to detect chlorophenols. These have included colorimetric methods, ultraviolet and infrared absorption, and paper, thin layer and gas chromatography. For trace analysis the colorimetric method with the 4-aminoantipyrine derivative and gas chromatography with electron capture have been the most widely used techniques. Some of those methods have been summarized in Table IV.

The colorimetric procedure is subject to criticism because of the many variables that may affect the analytical results. These include pH of the reactant solution, the time of color development, temperature, and instability of the color complex, as well as the fact that the chemical reaction applies to many phenols which give approximately the same adsorption maximum (Bevenue and Beckman, 1967).

Gas chromatography seems to be the most sensitive, rapid and specific method.

TABLE IV

Analytical Techniques Used for the Determination
of Chlorophenols in Trace Amounts

Author(s)	Quantitation Technique	Isolation Method	Compounds Studied	Type of Sample	Sensitivity or Limits of Detection	Remarks
Faust and Aly (1962)	Colorimetric 4-aminoantipyrine derivative pH 8.0	Acidify and extract with petroleum ether	2,4-dichlorophenol	water	7 to 70 μg/ℓ	Does not distinguish such compounds as *o*-chlorophenol and 2,4-dichlorophenol (*p*-substitution)
Aly (1968)	TLC 4-aminoantipyrine and *p*-nitrophenylazo derivative	Dye formation and then ether extraction	*o*-, *m*-, *p*-chlorophenol 2,4-dichlorophenol 2,6-dichlorophenol 2,4,6-trichlorophenol	water	1 to 5 μg/ℓ	Qualitative separation possible on one TLC plate
Bencze (1963)	Colorimetric 4-aminophenazone dye	Collection in basic solution with a sintered glass bubbler	pentachlorophenol and other lower chlorinated phenols	air	0.25 μg/ℓ of air	Interference from 2,3,5,6-tetrachlorophenol
Zigler and Phillips (1967)	TLC (2 directional) $AgNO_3$ development	Acidify and extract with petroleum ether	*m*-chlorophenol 2,4-dichlorophenol 2,4,5- and 2,4,6-trichlorophenol	water	0.1 μg/ℓ	
Kilgore and Cheng (1967)	GC-EC methyl ester	Acidify and extract with benzene	pentachlorophenol and sodium salt	fruits and nuts	0.01 ppm	
Stark (1969)	GC-EC methyl ester	Soil & fish - basic extraction-acidify steam distillation toluene extract. water-acidify, toluene extraction	pentachlorophenol	soil, fish, water	0.5 ppb in soil or fish 0.01 ppb in water	
Buhler *et al.* (1973)	GC-EC methyl ester	Acidify and extract with chloroform	pentachlorophenol	sewage and water	<0.01 ppb	
Barthel *et al.* (1969)	GC-EC methyl ester	Basic extraction, acidify, extract with benzene	pentachlorophenol	blood, urine, tissue and clothing	<0.01 ppm	
Cranmer and Freal (1970)	GC-EC alkyl ethers	Acidify and hexane extraction	pentachlorophenol	urine	2 ppb ± 5%	
Rivers (1972)	GC-EC methyl ether	Acidify and benzene extraction	pentachlorophenol	blood and urine	0.01 ppm	
Higgenbotham *et al.* (1970)	GC-EC no derivative	Liquid-liquid extractions	pentachlorophenol 2,3,4,6-tetrachlorophenol	fats, oils and fatty acids	0.5 ppm	
Shafik (1973)	GC-EC ethyl ether	Acidify and hexane extraction column chromatography	pentachlorophenol	human adipose tissue	5 ppb	
Baker (1965)	GC-EC no derivative	Freeze concentrated and hexane extraction	2,4-dichlorophenol	water	---	
Rudling (1970)	GC-EC acetate ester derivative	Hexane/*i*-propanol extraction	pentachlorophenol and other chlorophenols	fish tissues and water	0.1 ppb	
Kawahara (1971)	GC-EC pentafluorobenzyl ether derivative	---	*o*- and *p*-chlorophenol 2,4-dichlorophenol	water	<5 ppb	
Baker and Malo (1967)	Aqueous injection GC-FI	None	*o*-, *m*-, *p*-chlorophenol 2,3-, 2,4-, 4,5-, 2,6-, and 3,4-dichlorophenol	water	1 to 10 mg/ℓ	

VII. Chemical Reactivity

The chlorophenols are fairly weak acids, although they are stronger acids than phenol because of the chlorine atoms. They are converted to their sodium salts with sodium carbonate (unlike phenols) and this property affords a method of separating phenol from chlorophenols.

Generally, the chlorophenols react very similarly to phenol itself. They will form ethers, esters, and salts with metals, amines, etc. due to the phenol hydroxyl function. The aromatic function of chlorophenols will undergo substitution reactions such as nitration, alkylation, acetylation, halogenation, except when the aromatic ring is too highly substituted with chlorine.

The chlorine atoms can be hydrolized to polyhydroxyl benzenes with base at elevated temperatures and pressures. This is some times encountered during the synthesis of chlorophenols from chlorobenzenes.

Many of the chlorophenols can be oxidatively decomposed with strong oxidizing agents. Under some oxidative conditions the chlorophenols are transformed to the hydroquinone and benzoquinone. For example, oxidation of pentachlorophenol with nitric acid yields tetra-chloro-p-quinone (chloroanil) and tetrachloro-o-quinone.

Aqueous photolysis of chlorophenols for the most part leads to hydroxyl substitution for the chlorines and polymer formation. This is discussed in detail in Section IX A.

VIII. Biology

Very little biological information apart from toxicity data is available in the literature for any of the chlorophenol compounds except pentachlorophenol. In that extrapolation of biological processes (i.e., absorption, excretion, etc.) from toxicity studies can be misleading, reliance will be placed on studies specifically designed to monitor the various biological parameters.

A. Absorption

Both pentachlorophenol and sodium pentachlorophenate can be readily absorbed through the skin, with the sodium salt being appreciably more active (Dow Chemical, 1969c, 1969d). A ten minute exposure of hands to 0.4% pentachlorophenol has been shown to result in urine concentrations of 236 ppb (Benvenue, 1967a). In infants, residues of the sodium salt can be absorbed directly from linen in toxic amounts and can be reabsorbed from contaminated diaper urine (Armstrong _et_ _al_., 1969). Cutaneous absorption has been demonstrated in laboratory animals including rabbits and rats (Deichmann _et_ _al_., 1942). Absorption across the intestinal tract has been demonstrated in mice using ^{14}C-pentachlorophenol (Jakobson and Yllner, 1971). The widespread oral toxicity of pentachlorophenol indicates that such absorption is common after ingestion. Pentachlorophenol may also be directly absorbed by the aveolar surfaces in man in toxic amounts (Casarett _et_ _al_., 1969).

B. Excretion

Urinary elimination seems to be the primary mode of pentachlorophenol elimination in man, mice and rats. The amount and rate of pentachlorophenol excreted increases as the body content increases (Benvenue _et al_., 1967b). Although initial elimination may be rapid, complete elimination--i.e., to control levels--has been shown to take about one month (Benvenue _et al_., 1967a). In the mouse, 72-83% is excreted in urine over a four-day period. Most of the remaining compound is excreted in the feces with only trace amounts found in the expired air (Jakobson and Yllner, 1971). Similar results have been found in the rat. After a ten-day period, 65.2% is recovered in the urine and 3.1% in the feces. Trace amounts of respiratory excretion (0.4%) have been attributed to impurities of the initial pentachlorophenol (Larsen _et al_., 1972). Excretion studies on the lower chlorophenols have not been encountered.

C. Transport

From metabolic studies on the mouse, a probable scheme of pentachlorophenol transport has been postulated by Jakobson and Yllner (1971).

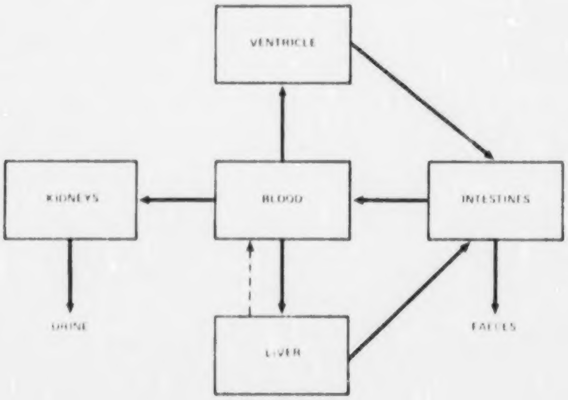


FIGURE 2
Pentachlorophenol Transport in the Mouse
[Jakobson and Yllner, 1971]

If modified to include entry into the blood from the skin and lungs, this diagram would seem to account for all transport in the mammalian system.

D. Distribution

Pentachlorophenol distribution data in humans comes almost entirely from autopsy reports of fatal intoxications.

TABLE V

Distribution of Pentachlorophenol in Three Cases of Fatal Intoxication

	Tissue	PCP (mg/100 g)
Case 1*	Kidney	2.8
	Adrenal	2.7
	Heart & Blood Vessel	2.1
	Fat	3.4
	Connective Tissue	2.7
Case 2**	Blood	5.0
	Urine	7.0
	Lung	14.5
	Kidney	9.5
	Liver	6.5
	Brain	2.0
Case 3**	Liver	Trace
	Stomach	-
	Kidney	-
	Spleen	-

* Armstrong et al., 1969

** Gordon, 1956

Needless to say, this data does not permit any conclusions. In non-fatal cases, however, there is evidence that pentachlorophenol may be bound to plasma protein but not to the blood cells (Casarett *et al.*, 1969).

In the mouse, the liver and intestines contain the highest amounts of residual pentachlorophenol with other organs accounting for only 0.2% of the original dose (Jakobson and Yllner, 1971). This is somewhat at variance with distribution studies in the rat showing that most of the accumulation is in the liver, kidney, and blood (Larson *et al.*, 1972). Distribution studies on lower chlorophenols and non-mammals have not been encountered.

E. Metabolism

Although Deichmann and coworkers (1942) indicated a possible metabolism of pentachlorophenol in mammalian systems, Jakobson and Yllner (1971) have proposed a metabolic route for the compound in mice.

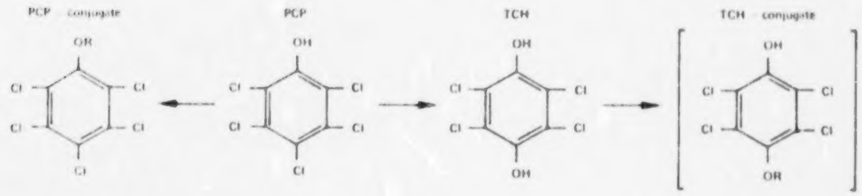


FIGURE 3
Suggested Metabolic Fate of PCP in Rats
[Jakobson and Yllner, 1971]

Although bacterial strains have been shown to degrade chlorophenols [see Environmental Fate and Transport section], further evidence for degradation in mammalian systems has not been found.

The potent molluscicide 2,2',3,3',5,5',6,6'-octachlorobiphenyl-quinone has been produced *in vitro* by oxidation of pentachlorophenol by a peroxidase found in snails. Whether this reaction proceeds *in vivo* and can account for the high toxicity of pentachlorophenol to snails was not indicated (Nabih and Metri, 1971).

F. Metabolic Effects

At concentrations as low as .1 ppm, pentachlorophenol radically affects the various enzyme systems in the fresh water eel *in vivo*. These effects stem mainly from the powerful uncoupling of oxidative phosphorylation. This causes an increase substrate demand by the respiratory cytochrome chain with subsequent increase in critic acid cycle activity (Boström and Johansson, 1972). This increase in activity is supported by a depletion of the fat deposits (Holmberg *et al.*, 1972). Weinbach (1957) has attempted to correlate the various *in vitro* metabolic effects of pentachlorophenol to its toxic activity as indicated in Table VI.

TABLE VI

Metabolic Effects of Pentachlorophenol and Their Possible Physiological Significance
[Weinbach, 1957]

Concentration of PCP	In Vitro Effect	Possible Physiological Significance
10^{-6}-10^{-4}M	Uncoupling of oxidative phyosphorylation	Interference with cellular aerobic exergonic processes
10^{-4}-10^{-3}M	Inhibition of mitochondrial ATPase	?
	Inhibition of myosin ATPase	Interference with phosphate transfer (and muscle function?)
10^{-3}M and higher	Inhibition of glycolytic phosphorylation Inactivation of respiratory enzymes Gross damage to mitochondrial structure	Rapid death of the cell and of the organism

The lower chlorophenols have been found to show similar biological activity. A series of mono- through tetrachlorophenols have been shown to uncouple oxidative phosphorylation with their potency roughly decreasing with decreased chlorination (Mitsuda et al., 1963).

TABLE VII

Inhibition of Oxidative Phosphorylation by Various Chlorophenols
[Mitsuda et al., 1963]

Chlorophenol	I_{50} (10^{-6}M)	pKa
Penta-(2,3,4,5,6,)	1	4.8
Tetra-(2,3,4,6,)	2	5.3
Tri- (2,4,5,)	3	7.0
Tri- (2,4,6,)	18	6.1
Di- (2,4,)	42	7.8
Di- (2,6,)	400	6.8
Mono- (2)	520	8.5
Mono- (3)	150	8.9
Mono- (4)	180	9.2
2,4-Dinitrophenol	17	4.0
Phenol	5000	10.0

Similarly, some lower chlorophenols have been shown to inhibit catalase activity (Goldacre and Galston, 1953). Here, however, no clear correlation can be drawn between the degree of chlorination and potency as indicated in Table VIII.

TABLE VIII

50% Inhibition of Catalase Activity by
Various Chlorophenols
[Goldacre and Galston, 1953]

Phenol	I_{50} (M)
o-chloro	4×10^{-5}
m-chloro	2×10^{-4}
p-chloro	7×10^{-5}
2,4-dichloro	2×10^{-6}
2,5-dichloro	2×10^{-5}
2,4,6-trichloro	1×10^{-2}

The toxicologic significance of these metabolic effects must await a more complete definition of the toxic properties of the various lower chlorophenols.

IX. Environmental Transport and Fate

A. Persistence and/or Degradation

The stability of chlorophenols in the environment has received a great deal of study because the compounds are well recognized contaminants. They have also received detailed study when it became recognized that they were major metabolites of pesticide by-products which utilize chlorophenols as a raw material (Loos _et al._, 1967a; Loos _et al._, 1967b; Alexander and Aleem, 1961). Both the photodecomposition and the biodegradation will be discussed.

In terms of biological degradations, three general conclusions have been reached: (1) the chlorophenols are much more environmentally stable than the parent phenol (Ingols _et al._, 1966); (2) as the number of chlorine atoms increases the rate of decomposition seems to decrease (Cambers _et al._, 1963); and (3) compounds containing a _meta_-substituted chlorine are more persistent than compounds lacking a _meta_-substituted chlorine (Alexander and Aleem, 1961).

The experimental conditions in these types of studies vary considerably and quite often some of the results conflict with the above general conclusions. Alexander and Aleem's (1961) study of the decomposition of chlorophenols by soil microbes is the most comprehensive in terms of the number of compounds studied. They monitored spectrophotometrically the disappearance of substrate in aqueous solutions (50 mg/ℓ) with a soil microbial inoculum. The results are presented in Table IX. The 3-substituted phenols were always resistant to microbial decomposition and the authors suggest that this explains the greater persistence in field soil of 2,4,5-T when compared to 2,4-D.

TABLE IX

Microbial Decomposition of
Chlorophenols in Soil Suspensions
[Alexander and Aleem, 1961]

Compound	Wavelength nm	Days for Complete Disappearance	
		Dunkirk Soil	Mardin Soil
Phenol	269	2	1
2-Chlorophenol	274	14	47
3-Chlorophenol	274	72+	47+
4-Chlorophenol	279	9	3
2,4-Dichlorophenol	283	9	5
2,5-Dichlorophenol	279	72+	-
2,4,5-Trichlorophenol	288	72+	47+
2,4,6-Trichlorophenol	288	5	13
2,3,4,6-Tetrachlorophenol	300	72+	-
Pentachlorophenol	320	72+	-

Chambers et al. (1963) examined the oxygen uptake of phenol-adapted cultures which were exposed to chlorophenol substrates. Figure 4 demonstrates the retarding effect of chlorine substitution.

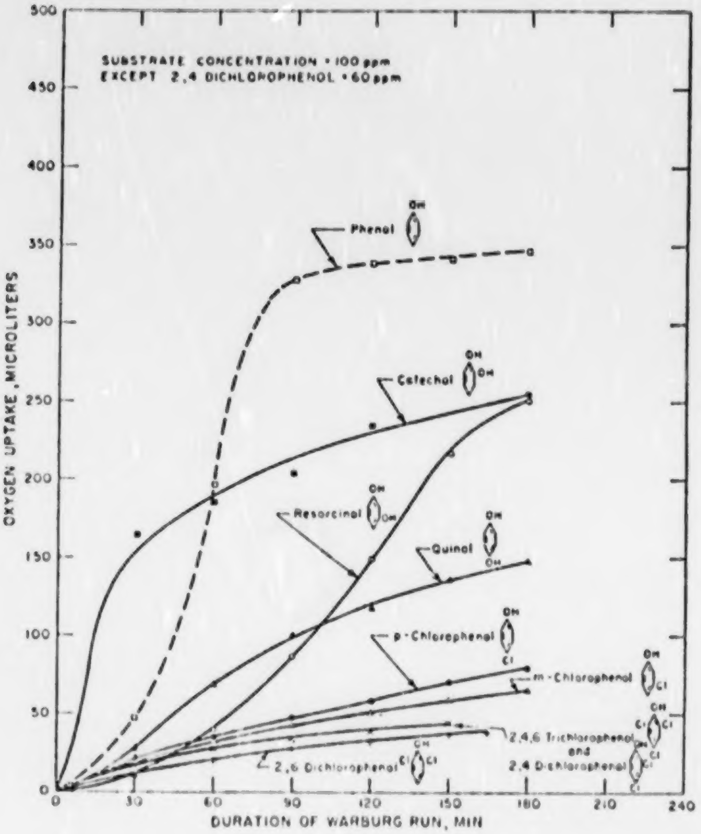


FIGURE 4
Oxidation of Hydroxy- and Chlorophenols
[Chambers _et_ _al_., 1963];
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Journal Water Pollution Control Federation.

Alexander and Lustigman (1966) studied monochlorophenols under conditions similar to Alexander and Aleem (1961). Again, they found that chlorophenols degrade slower than phenol and the _p_-chlorophenol appears to degrade fastest (see Table X).

TABLE X

Decomposition of Phenol and
Chlorophenol by a Soil Microflora
[Alexander and Lustigman, 1966]

Compound	Wavelength	Days for Complete Disappearance
Phenol	-	1
o-Chlorophenol	274	764
m-Chlorophenol	274	764
p-Chlorophenol	279	16

In contrast, Walker (1954) using a soil percolator system found that *o*-chlorophenol and not *p*-chlorophenol was the only compound degraded. However, Beveridge and Tall (1969), in agreement with Alexander and Lustigman (1966), showed that only *p*-chlorophenol could be degraded by a phenol oxidizing bacterium (NCIB 8250).

Ingols *et al*. (1966) studied the biodegradation of chlorophenols with acclimated sludge. Their results are summarized in Table XI and agree fairly well with the generalizations cited previously.

TABLE XI

Maximum Degradation Obtained
for Each Compound at 100 mg/ℓ
[Ingols *et al*., 1966]

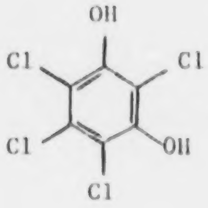
Compound	Ring Degradation %	Time (Days)	Halide Ion Development %	Halide Ion Development Time (days)
o-chlorophenol	100	3	100	4
m-chlorophenol	100	2	100	3
p-chlorophenol	100	3	100	3
2,4-Dichlorophenol	100	5	100	5
2,5-Dichlorophenol	52	4	16	4
2,4,6-Trichlorophenol	100	3	75	3
Na 2,3,4,5,6-Pentachlorophenol	0	4	0	4

Pentachlorophenol has received more detailed study than the other chlorophenols because of sizable quantities used directly as herbicides or fungicides. Ide *et al*. (1972) studied PCP decomposition in rice fields. They found that under rice field conditions reductive dechlorination occurred and resulted in the following stable metabolites: 2,3,4,5-, 2,3,5,6-, and 2,3,4,6-tetrachlorophenol, 2,4,5- and 2,3,5-trichlorophenol, 3,4- and 3,5-dichlorophenol, and 3-chlorophenol. Interestingly enough, these all contain a *meta*-chloro substitutent, a structure reported to be extremely persistent by Alexander and Aleem (1961).

Kirsch and coworkers (Kirsch and Etzel, 1973; and Chu and Kirsch, 1972) have isolated bacteria that are capable of degrading and using PCP as an energy and carbon source. However, the PCP-oxidizing organisms are slower growing than other organisms and when other nutrient supplies are available the PCP oxidation rate is lower, thus suggesting that, under normal environmental conditions, PCP may still be quite persistent.

The photodecomposition of 2,4-dichlorophenol and pentachlorophenol with sunlight has been reported. Crosby and Tutass (1966) in a study of 2,4-D detected 2,4-dichlorophenol as a major photolysis product. The phenol was further photooxidized to 4-chlorocatechol and then to 1,2,4-benzenetriol which is air oxidized to polyquinoid humic acids. The importance of this pathway to the environmental decomposition of dichlorophenol is unknown, although practical tests indicate that sunlight does have an effect on 2,4-D in the field.

Munakata and Kuwahara (1969) showed that the toxicity of pentachlorophenol in rice field water could be prolonged by covering the surface of the field with sheets to shut out the sunshine. They also demonstrated that 50% of a 1 Kg solution of PCP in 50 liters of water decomposed in ten days when irradiated with sunlight. The following intermediate products were isolated as well as large amounts of resineous materials.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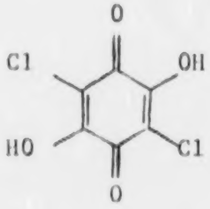
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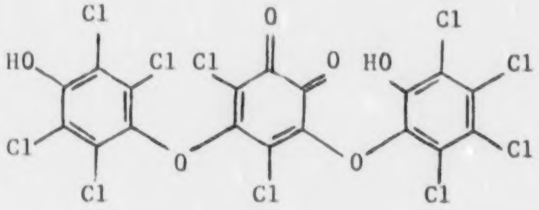
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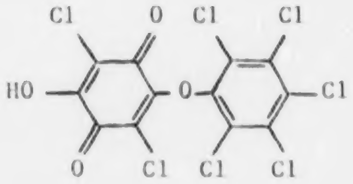
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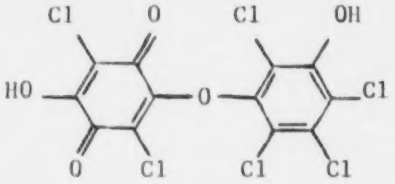
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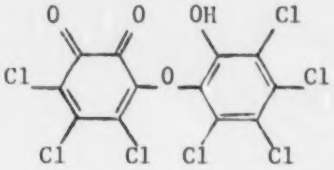
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B. Environmental Transport

Mass balances and flow diagrams of chlorophenol transport through the environment are not available because of the general lack of monitoring data. Their moderate volatility (PCP 0.00011 mm Hg) would suggest that atmospheric transport may be a significant route. However, for the most part, they are considered water and soil contaminants.

C. Bioaccumulation

Pentachlorophenol appears to accumulate in the fatty tissues of various species. Significant concentrations are found in human adipose tissue (Shafik, 1973). Levels of 105 to 110 ppm have been detected in guppies exposed to water containing 3 ppm PCP. Also, levels of from 0.2 to 3 mg/kg flesh tissue were found in fish samples in a lake containing 3 μg/ℓ. Highest concentrations were found in the high fat content species.

Bioaccumulation data on other chlorophenols is not available.

X. Toxicity

A. Human Toxicity

Information on pentachlorophenol and its sodium salt comprise by far the greater part of the available human toxicity data. Because of the lack of human toxicity information on the lower chlorophenols, it is difficult to determine to what extent the preponderance of the pentachlorophenols is due to an inherently greater human toxicity of the pentachloro-compounds and/or to differences in the frequency and intensity of human exposure to the various chlorinated phenols. As the subsequent sections on non-human life forms will indicate, all of the studied chlorophenols show some degree of toxicity. However, with the exception of an isolated report of increased neuromuscular excitability and decreased thermoregulatory ability associated with occupational exposure to p-chlorophenol (Gurova, 1964), 2,4,5-trichlorophenol and pentachlorophenol are the only compounds listed in the literature as having caused human toxic responses.

Technical grade 2,4,5-trichlorophenol can cause irritation to the eyes, skin, nose, and throat. Depending on the degree of exposure, ocular damage may include the conjunctiva, iris, and/or cornea with the damage varying from slight irritation to chemical burns (Dow Chemical Company, 1969a). Skin contact may result in mild to moderate chemical burns or chloracne (Kimbrough, 1972). However, technical grade 2,4,5-trichlorophenol may contain a number of impurities including tri- and tetrachlorodibenzofuran and tetrachlodibenzodioxine. These impurities may well be the causative agents of chloracne (Kimmig and Schulz, 1957). In follow-up studies on cases of 2,4,5-trichlorophenol induced chloracne, there may be evidence of psychopathology expressed in decreased mental and physical activity (Kleu and Göeltz, 1971). Similar studies have been reported by Kimbrough (1972) implicating liver damage as part of the long-term exposure effects. Compared to the trichlorophenol, sodium 2,4,5-trichlorophenate has toxic properties similar in kind but somewhat more intense in degree (Dow Chemical Company, 1969b).

Cases of pentachlorophenolic poisoning most often involve dermal exposure although inhalation can also be pathogenic (Cassaret _et al._, 1969). Sodium pentachlorophenate which is much more readily absorbed through the skin than the phenol (Dow Chemical, 1969c, 1969d) is usually indicated as the toxic agent. Although the toxic properties of both the phenol and the sodium salt had been defined in the early 1940's using laboratory animals (Deichmann _et al._, 1942), cases of human toxicity were not reported until the following decade. Five fatal cases are reported involving the use of spray applicators with concentrations of 1.0%-14.0% sodium pentachlorophenate. The clinical signs include profuse sweating, thirst, elevated temperature, rapid pulse and respiration, abdominal pain, and death within about 24 hours after the first symptoms develop (Gordon, 1956). Similar poisonings have resulted from manual submersion of wood into solutions of sodium pentachlorophenate. Nine such deaths have been reported after exposure to 1.5%-2.0% solutions over a 3-30 day period. The disease was characterized by elevated body temperature (101^{o}-108^{o}F), labored breathing, extreme sweating, and a general increase in the basal metabolic rate (BMR) due to uncoupling of oxidative phosphorylation (Menon, 1958). Bergner and associates (1965), in studying similar cases, indicate that death may be caused by elevated temperature, fluid loss, or cardiac arrest with histological damage to both the kidney and liver. More recently, nine infants were poisoned by sodium pentachlorophenate residues on laundry which led to two fatalities. In this case, the laundry soap contained 22.9% sodium pentachlorophenate which remained in amounts of 1.15-195.0 mg/100 g in the diapers, blankets, and other nursery linen. This compound was absorbed by the infants reaching serum levels of 118 mg/kg causing severe illness after five days exposure. In that urinary excretion is a prime mode of chlorophenol elimination, the immature renal functions of neonates and PCP reabsorption from diaper urine may have facilitated toxic accumulation (Armstrong, et al., 1969). As of 1969, thirty fatal cases of pentachlorophenol poisoning had been reported (Robson et al., 1969).

Non-fatal exposures commonly involve irritation of the eyes, skin and upper respiratory tract similar to that outlined for 2,4,5-trichlorophenol. In addition, less severe systemic disorders of the kind described in fatal cases are also noted (Bergner et al., 1965). Symptoms may be elicited by seemingly small exposures. In one case, immersion of hands for 10 minutes in a 0.4% solution of pentachlorophenol caused severe pain and inflammation (Benvenue et al., 1967a).

Similarly, bathing in water containing 12.5 ppm pentachlorophenol over a 13-day period caused facial inflammation, increased temperature and pulse rate, and intermittent delerium (Chapman and Robson, 1965).

B. Toxicity to Birds and Non-human Mammals

1. Acute Toxicity

Mammalian systems have been used to test the toxicity of a number of chlorophenols in an attempt to extrapolate the human toxic potential of these compounds. Emphasis has been placed both in comparing the animal response with the human response and on establishing the relative toxicities of the chlorophenols.

Median lethal doses (LD_{50}) have been used as a criterium with which to compare the toxicities of various compounds. Such data is presented in Table XII for the acute oral toxicity of various chlorophenols to laboratory animals.

TABLE XII

LD_{50}'s of Various Chlorophenols and Sodium Chlorophenates After a Single Oral Administration

Phenol Compound	Animal	LD_{50} (mg/kg body weight)	Reference
p-chloro-	rat	500	Gurova, 1964
o-chloro-	blue fox	440	Bubnov _et_ _al_., 1969
"	mice	670	"
2,4-dichloro-	rat (male)	3600	Kobayaski _et_ _al_., 1972
"	rat (female)	4500	"
"	mice	1630	"
2,4,5-trichloro-	rat (male)	2830	Dow Chemical, 1969a
"	rat (female)	2460	"
"	rat	2960	McCollister _et_ _al_., 1961
Na 2,4,5-trichloro-	rat (male)	1870	Dow Chemical, 1969b
"	rat (female)	1620	"
Pentachloro-	rabbit	70-130*	Deichmann _et_ _al_., 1942
"	rat	27.3-77	"
"	rat (male)	205	Dow Chemical, 1969d
"	rat (female)	135	"
Na Pentachloro-	rabbit	250-300*	Deichmann _et_ _al_., 1942
"	"	275	Dow Chemical, 1969c
"	rat	210.6	Deichmann _et_ _al_., 1942
"	"	210	Dow Chemical, 1969c
"	guinea pig	80-160	"

*Minimum Lethal Concentration

Similar information on the acute LD_{50}'s from intraperitoneal injections is available from the work of Farquharson and associates (1958), and is summarized in Table XIII.

TABLE XIII

Acute LD_{50}'s of Chlorophenols Determined by Intraperitoneal Injection to Male Albino Rats [Farquharson *et al.*, 1958]

Number of Chlorine Atoms	Phenol	LD_{50} (mg/kg)
1	o-chloro-	230
	p-chloro-	281
	m-chloro-	355
2	2,6-dichloro-	390
	2,4-dichloro-	430
3	3,4,5-trichloro-	372
	2,4,5-trichloro-	355
	2,3,6-trichloro-	308
	2,4,6-trichloro-	276
4	2,3,4,6-tetrachloro-	130
5	2,3,4,5,6-pentachloro-	56

This data indicates a sharp decrease in toxicity going from the mono- to di-chlorinated phenols and then a progressive increase in toxicity with greater chlorination.

Pathological data on the lower chlorophenols is sketchy. At lethal concentrations, *o*-chlorophenol causes fatty degeneration of the liver, renal granular dystrophy, and necrosis of the stomach and intestinal mucosa (Bubnov, *et al*., 1969). In intraperitoneal injections, the monochlorophenols, 2,6-dichlorophenol, and 2,4,6-triphenol elicited similar responses including initial excitation, tremors in 40-120 seconds, followed by convulsions, loss of righting reflex and death. The higher chlorophenols led to rapid prostration without tremors (Farquharson *et al*., 1958). With oral administration of pentachlorophenol, increases were noted in temperature, blood pressure and initial urinary output. Muscular weakness developed and autopsy indicated extensive vascular damage and heart failure (Deichmann *et al*., 1942).

Studies on dermal exposure have not been encountered for the lower chlorophenols. Both 2,4,5-trichlorophenol and its sodium salt have been shown to cause a slight reddening of rabbit skin after brief exposures and mild to moderate chemical burns with longer exposures (Dow Chemical, 1969a and b; McCollister *et al*., 1961). As in human toxicity, cutaneous absorption of sodium pentachlorophenate can be fatal. Lethal doses for rabbits have been reported as low as 250 mg/kg in 10% aqueous solution

(Deichmann *et al*., 1942). Median lethal doses range between 100-300 mg/kg applied as a 20% solution (Dow Chemical, 1969c).

Pentachlorophenol is reported to be less readily absorbed by the skin. At doses of 50-100 mg/kg, Dow Chemical (1969d) reports 100% survival in rabbits. Deichmann and associates (1942), however, report lethal concentrations as low as 40 mg/kg. It must be kept in mind that this discrepancy may well be due to impurities in the earlier sample. Both pentachlorophenol and sodium pentachlorophenate have been shown to cause chloracne in rabbits (Dow Chemical, 1969c, 1969d).

2. Chronic Toxicity

Long-term feeding studies have been conducted on di-, tri-, and pentachlorophenols. With dietary feeding of 2,4-dichlorophenol at a concentration of 0.1% over a six-month feeding period, no adverse effects were noted in rats (Kobayaski *et al*., 1972). In rats fed up to 0.1g/kg/day 2,4,5-trichlorophenol, no adverse effects were noted over a three-month period. At dosages of 1g/kg/day, weight loss and degenerative changes of the kidney and liver were observed (McCollister *et al*., 1961). Rats fed 5mg/day over a six-month period failed to grow and doses of 3.9mg/day caused retarded growth (Deichmann *et al*., 1942).

3. Sensitization

Although sensitization can be developed in humans exposed to sodium pentachlorophenol, no similar sensitization has been reported in lower mammals (Dow Chemical, 1969c). McCollister and associates (1961) report no sensitization to 2,4,5-trichlorophenol.

4. Teratogenicity

No studies encountered.

5. Carcinogenicity

No studies encountered.

6. Mutagenicity

No studies encountered.

7. Behavioral Effects

No studies encountered.

C. Toxicity to Lower Animals

Toxicity data on the lower animals is based primarily on the bony fishes. Although most of the information available is on pentachlorophenol, the TLm's of some of the lower chlorophenols have been determined. In fish, these chlorophenols seem to exhibit a reverse order of toxicity from that shown in mammalian systems, as indicated in the following table.

TABLE XIV

Comparison of LD_{50}'s for Intraperitoneal
Injection in Rats
[Farquharson _et_ _al_., 1958]
to 24 Hour TLm of Fishes
[Ingols _et_ _al_., 1966]

Phenol Compound	TLm (mg/ℓ)	LD_{50}(mg/kg)
o-chloro-	58	230
m-chloro-	18	355
p-chloro-	14	281
2,4,6-trichloro-	3.2	276
"	1.0-0.1*	

*96-hour TLm for fathead minnow (Manufact. Chem. Assoc., 1972).

For the fish, the toxicity seems to increase with oil solubility and indicates that the primary mechanism of toxicity involves the dissolving of fatty tissue by the toxicant (Ingols _et_ _al_., 1966). This scheme seems consistent with the almost 100% increase in fatty acid catabolism noted in salmon after a 14-day exposure to 0.1 mg/ℓ potassium pentachlorophenate (Hanes _et_ _al_., 1968). The 24 hour TLm for sodium pentachlorophenate to the fathead minnow is 0.32-0.35 mg/ℓ (Crandell and Goodnight, 1959). Other species of fish seem even more sensitive to this compound as indicated in Table XV.

TABLE XV

Median Tolerance Limits of Some Fresh Water Fishes to Sodium Pentachlorophenate
[Matida *et al.*, 1970]

	(Observed TLm (Na-PCP, p.p.m.)						Ultimate TLm	Body	Temp.
	6 hr.	12 hr.	24 hr.	48 hr.	96 hr.	240 hr.	estimated	wt., g	°C
Rainbow trout			0.07	0.056	0.049	0.048	0.0475	0.73	17.2±0.4
Common carp	0.295	0.195	0.135	0.13	0.13	0.13	0.125	1.36	25.9±0.5
Southern top-monthed minnow			0.17	0.16	0.16	0.16	ca 0.16	0.8	25.2±0.5
Sweet fish			0.086	0.068	0.068		ca 0.068	1.9	17.9±0.6

Similar to the effects noted in mammals, pentachlorophenol at 0.1 mg/kg caused an increase in the metabolic rate and liver enlargement in the eel (Holmberg *et al.*, 1972). An important point in environmental considerations is that the toxicity of pentachlorophenol increases as the pH nears the pK. Thus, organisms in an alkaline aquatic environment could better tolerate pentachlorophenol than could an organism in acidic medium (Crandall and Goodnight, 1959).

D. Toxicity to Plants

The chlorophenols have a wide range of phytotoxicity. Perhaps the most significant studies are those concerning the lower plants. Blackman and coworkers (1955a) have determined the LD_{50}'s for a number of chlorophenols on the green water plant *Lemna minor* using the concentration which caused chlorosis in half the fronds as the index of toxicity. The results are given in Table XVI.

TABLE XVI

LD_{50}'s of Various Chlorophenols on Lemna minor
[Blackman et al., 1955a]

Phenol	moles/ℓ	mg/ℓ
p-chloro-	2.2×10^{-3}	282.7 mg/ℓ
2,4-dichloro-	3.6×10^{-4}	58.7 mg/ℓ
2,4,6-trichloro-	3.0×10^{-5}	5.92 mg/ℓ
2,4,5-trichloro-	8.4×10^{-6}	1.65 mg/ℓ
2,3,4,6-tetrachloro-	2.6×10^{-6}	.61 mg/ℓ
2,3,4,5,6-pentachloro-	7.1×10^{-7}	.19 mg/ℓ

Further, a linear relationship exists between the logarithms of the LD_{50} and the solubility of the chlorophenols as indicated in Figure 5 (Blackman et al., 1955b).

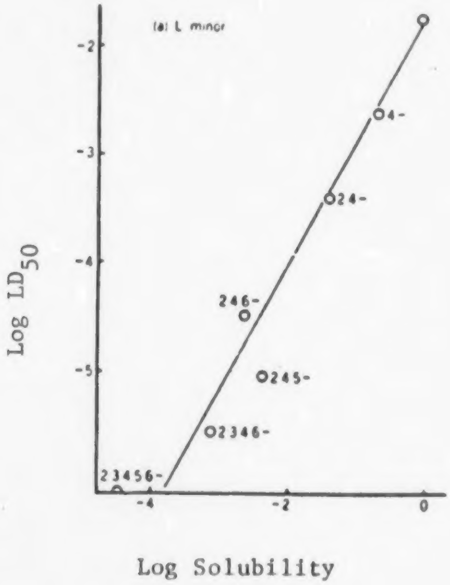

FIGURE 5
Relationship Between the Logarithm of
the Solubility of Chlorophenols and the LD_{50} in Lemna minor
[Blackman et al., 1955b];
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This seems to indicate that the physiological effect is increased as the pH of the medium approaches the pK of the chlorophenol (Crandell and Goodnight, 1959). This conclusion has been verified by Fujita and Nakajima (1969) for a wide range of biological activities. Similar generalizations might be found valid for higher plants if proper screening tests were conducted. Toxic responses have been elicited in pea stems with 2,3,6-trichlorophenol, whereas 2,6-dichlorophenol has greater growth stimulating properties (Harper and Wain, 1969). Pentachlorophenol, 2,4-dichlorophenol, and p-chlorophenol have been shown to cause abnormal mitoses in _Vicia faba_, the European Broad Bean (Amer and Ali, 1969). However, only pentachlorophenol has been implicated in whole plant toxicity. Pentachlorophenol causes considerable malformation in crested wheatgrass seedlings at concentrations of 2-4 lb/acre (Klomp and Hull, 1968). Although pentachlorophenol has been used extensively as a desiccant (Bovey, 1969) and weed-killer (Hilton _et al_., 1970), similar malformations have not been noted.

E. Toxicity to Microorganisms

Similar to their work on _Lemna minor_, Blackman and coworkers (1955a) have determined the toxicity of various chlorophenols to the mold _Trichoderma viride_, using the concentration required to halve the growth rate as the standard.

TABLE XVII

Concentrations of Various Chlorophenols Required for 50% Inhibition of Radial Growth (IC_{50}) for *T. viride*

[Blackman et al., 1955a]

Phenol	Moles/ℓ	mg/ℓ
p-Chloro	3.7×10^{-4}	47.5 mg/ℓ
2,4-dichloro	5.3×10^{-5}	8.64 mg/ℓ
2,4,6-trichloro	3.5×10^{-5}	6.97 mg/ℓ
2,3,4,6-tetrachloro-	3.4×10^{-6}	.80 mg/ℓ
2,3,4,5,6-pentachloro-	1.2×10^{-6}	.32 mg/ℓ

Again, a linear relationship was demonstrated between the logarithms of the IC_{50}s and solubilities of the chlorophenols.

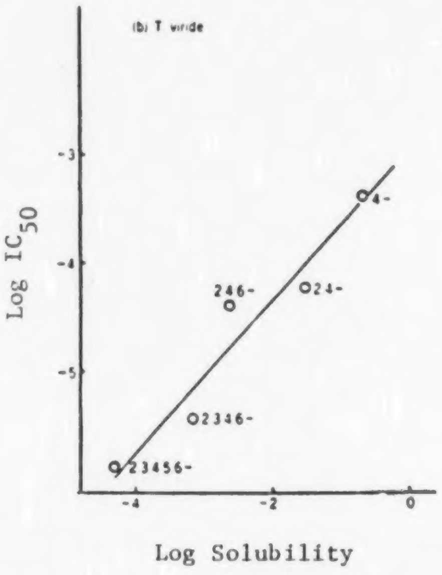

FIGURE 6

Relationship between the Logarithm of the IC_{50} and the Solubilities of Some Chlorophenols [Blackman *et al.*, 1955b]; reprinted by permission. Copyright 1955, Academic Press.

This interpretation of toxicity in terms of physical structure gives much more satisfactory results than the phenol coefficient method used by Wolf and Westveer (1952) which indicated a low order of toxicity for pentachlorophenol. In fact, pentachlorphenol has been found highly toxic to a wide variety of microorganisms as indicated in Table XVIII.

TABLE XVIII

Antimicrobial Efficiencies of Pentachlorophenol
(Dowicide EC-7) [Dow Chemical, no date]

Test Organism	% DOWICIDE EC-7 for Inhibition
Trichoderma viride, ATCC#8678	0.0025-0.005
Trichoderma sp., Madison P-42	0.001-0.0025
Ceratocystis pilifera, ATCC#15457	0.0005-0.001
Polyporus tulipiferae, ATCC#11245	Less than 0.0001
Rhizopus stolonifer, ATCC#6227a	0.0001-0.00025
Lenzites trabea, Madison 617	0.0001-0.00025
Ceratocystis ips, ATCC#12860	0.001-0.0025
Chaetomium globosum, ATCC#6205	0.0001-0.00025
Aspergillus niger, ATCC#6275	0.001-0.0025
Bacillus cereus var. mycoides, ATCC#11778	0.0005-0.001
Bacillus subtilis, ATCC#8473	0.005-0.01
Escherichia coli, ATCC#11229	0.025-0.05
Pseudomonas aeruginosa, ATCC#15442	0.1-0.25
Enterobacter aerogenes, ATCC#13048	0.05-0.1
Streptomyces griseus, ATCC#10137	0.0005-0.001
Flavobacterium arborescens, ATCC#4358	0.00025-0.0005

Other studies have found that the lower chlorophenols also can inhibit microbial activity. The oxygen uptake of a mixed microbial population is significantly inhibited by 2,4,6-trichlorophenol concentrations of 50 mg and 100 mg/ℓ of synthetic sewage but not a 1 and 10 mg/ℓ (Manufact. Chem. Assoc., 1972). The growth of the fungus *Aspergillus niger* is inhibited by 50% at concentrations of 77.9 mg/ℓ (4.5 x 10^{-4}M) p-chlorophenol and 1800 mg/ℓ (14 x 10^{-4}M) o-chlorophenol (Shirk and Corey, 1952; Shirk *et al.*, 1951).

XI. Chlorophenols: Summary and Conclusions

The chlorophenols and their salts comprise an important class of biocides and chemical preservatives. Although production information is somewhat fragmentary, the chlorophenol market seems for the most part in a state of flux. Pentachlorophenol is easily the most important compound in this class with an annual production of over 50 million pounds and a predicted growth rate of 4% per year. Although the 2,4 dichlorophenol market may be dwindling, it is still a significant intermediate in the formation of 2,4-D and may currently be produced in quantities of over 50 million pounds annually. The 2,4,5-trichlorophenol market may also be decreasing but production figures are still probably in the tens of millions of pounds annually. The production of p-chlorophenol cannot be accurately estimated.

For the most part, all of these compounds are used as biocides or as raw material in the formation of other biocides or chemical preservatives. The probability of environmental contamination from these uses is, of course, high. As molluscacides (PCP), insecticides, or antimicrobials, they are often released directly into the environment. Used as preservatives for wood, leather, or latex, the probability of leaching seems evident. Release from water treatment plants, industrial cooling systems, or biodegradation of herbicides (2,4-D and 2,4,5-T) may also be important sources of contamination. Monitoring data would tend to support the above conclusions. 2,4-dichlorophenol has been found in the environment in the low ppb range. Pentachlorophenol is already wide-spread at concentrations in the high ppb and low ppm range in some parts of the country as evidenced by direct monitoring data and human urinalysis. Although the common uses of the chlorophenols would seem to indicate environmental transport primarily by soil and water, the intermediate volatilities of the chlorophenols would allow for some degree of atmospheric transport. Such transport may account for the presence of chlorophenols in areas not receiving direct exposure.

Once in the environment, in sufficient amounts, there can be little doubt these compounds will have deleterious effects on a wide range of life forms. All of the chlorophenols have been found capable of uncoupling oxidative phosphorylation and inhibiting some enzyme systems. Pentachlorophenol is clearly the most powerful biocide. It is toxic to mammals over short periods at 10 ppm. The long term tolerance for some fish has been estimated at .05-.16 ppm. Similarly, lower plants and microorganisms respond adversely in the .1 ppm range. Most significantly, pentachlorophenol has been shown to bio-accumulate in fish. Similar accumulations in mammals are probable. The lower chlorophenols seem to decrease in biological activity with decreased chlorination. Although their mammalian toxicity may be low (>1000 ppm), species of fish, plants, and microorganisms are injuriously effected by trichlorophenols in the 1 ppm range and monochlorophenols in the 10 ppm range.

Although the production, uses, and biocidal properties of the chlorophenols indicate a potential for environmental hazard, a final determination is somewhat dependent on the degree of chlorophenol persistence.

Generally, decomposition tends to decrease with increased chlorination and meta-substitution. Physical degradation, especially photodecomposition, may be major route, but a reliable quantitative estimation cannot be made. In the same way, a number of microorganisms have demonstrated the ability to metabolize chlorophenols under ideal conditions but the rate at which this occurs in the environment is not certain. Some studies indicate persistence time may be measured in weeks. However, the possibility that the chlorophenols are removed from the samples by biological uptake and transport rather than biological degradation cannot be ruled out.

The potential for environmental hazard from the chlorophenols seems clear. Pentachlorophenol, without doubt, poses the greatest danger. It has the greatest production and most obvious exposure to the environment. It is certainly the most toxic and probably the most persistent. Although less is known about the lower chlorinated phenols, they cannot be discounted. Almost all of the chlorophenols are commercially successful because they are toxic in some way. That this toxicity might extend beyond the bounds for which it is intended seems a reasonable possibility.

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